

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE  
COMPANY, JOHN HANCOCK  
VARIABLE LIFE INSURANCE  
COMPANY and MANULIFE  
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

**ABBOTT'S CORRECTED DEPOSITION DESIGNATIONS AND  
COUNTER DESIGNATIONS FOR JAMES THOMAS, Statistician (ABT-594)**

Defendant Abbott Laboratories ("Abbott") respectfully submits the attached deposition designations and counter-designations for the April 13, 2007 deposition of James Thomas, Statistician (ABT-594).

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Dated: February 22, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By:     /s/ Eric J. Lorenzini      
Eric J. Lorenzini

Jeffrey I. Weinberger (*pro hac vice*)  
Gregory D. Phillips (*pro hac vice*)  
Eric J. Lorenzini (*pro hac vice*)  
Ozge Guzelsu (*pro hac vice*)  
MUNGER, TOLLES & OLSON LLP  
355 South Grand Avenue, Thirty-Fifth  
Floor  
Los Angeles, CA 90071-1560  
Tele: (213) 683-9100

and

Peter E. Gelhaar (BBO#188310)  
Michael S. D'Orsi (BBO #566960)  
DONNELLY, CONROY &  
GELHAAR LLP  
1 Beacon St., 33<sup>rd</sup> Floor  
Boston, Massachusetts 02108  
(617) 720-2880  
peg@dcglaw.com  
msd@dcglaw.com

*Counsel for Abbott Laboratories*

**CERTIFICATE OF SERVICE**

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 22, 2008.

Date: February 22, 2008.

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/s/ Ozge Guzelsu

## James Thomas Deposition Designations

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
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<b>Depo Date</b>	<b>Witness</b>	<b>Hancock Designation</b>	<b>Abbott Counter Designation</b>	<b>Abbott Designation</b>	<b>Deposition Exhibit</b>	<b>Plaintiff Exhibit</b>	<b>Defendant Exhibit</b>
04/13/07	Thomas, James		61:15-62:2				
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## Color Key to Deposition Designations

 Designation by Plaintiffs

 Counter Designation by Defendants

 Designation by Defendants

Thomas, James (Linked) 4/13/2007 8:05:00 AM

1 THE UNITED STATES DISTRICT COURT  
2 FOR THE DISTRICT OF MASSACHUSETTS  
3  
4 JOHN HANCOCK LIFE INSURANCE )  
5 COMPANY, JOHN HANCOCK VARIABLE )  
6 LIFE INSURANCE COMPANY, and )  
7 MANULIFE INSURANCE COMPANY )  
8 (f/k/a INVESTORS PARTNER ) Civil Action  
9 INSURANCE COMPANY), ) No.  
10 Plaintiffs, ) 05-11150-DPW  
11 -vs- )  
12 ABBOTT LABORATORIES, )  
13 Defendant. )

14  
15 The videotaped deposition of JAMES THOMAS,  
16 called as a witness herein for examination, taken  
17 pursuant to the Federal Rules of Civil Procedure of  
18 the United States District Courts pertaining to the  
19 taking of depositions, taken before ROSANNE M.  
20 NUZZO, a Notary Public within and for the County of  
21 Will, State of Illinois, and a Certified Shorthand  
22 Reporter of said state, at Suite 1300, Two North  
23 LaSalle Street, Chicago, Illinois, on the 13th day  
24 of April, A.D. 2007, at approximately 8:05 a.m.

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1 A. Okay.

2 Q. If you need a break at any time, let us  
3 know, and we'll try to accommodate you.

4 A. Okay.

5 MR. ZWICKER: Okay?

6 Greg, usual stipulations we've done so  
7 far?

8 MR. PHILLIPS: Yes.

9 MR. ZWICKER: Okay.

10 BY MR. ZWICKER:

11 Q. Mr. Thomas, where do you work?

12 A. Abbott Laboratories.

13 Q. What's your job there?

14 A. I'm a manager in statistics.

15 Q. How long have you had that job -- that  
16 title?

17 A. That title? Two years, roughly.

18 Q. What are your responsibilities as  
19 manager of statistics?

20 A. I am in charge of reviewing protocols,  
21 reviewing case report forms, clinical physical  
22 reports, helping design studies for clinical  
23 trials in phase 2 and phase 3 studies of new  
24 medications and to supervise other statisticians



1 who are working on my project.

2 Q. In your present job, how many  
3 statisticians do you supervise?

4 A. Currently, four.

5 Q. Who do you report to in your present  
6 job?

7 A. Yili Pritchett.

8 Q. Spell it for the record.

9 A. Y-i-l-i, P-r-i-t-c-h-e-t.

10 Q. Is David Morris still employed at  
11 Abbott?

12 A. He is not.

13 Q. You reported to him at some point,  
14 didn't you?

15 A. I did.

16 Q. How many clinical trials are you  
17 working on now? Approximately?

18 A. Oh. Approximately, six.

19 Q. Before you were manager of  
20 statistics -- let me strike that.

21 You began as manager of statistics in  
22 approximately 2005?

23 A. Yes.

24 Q. Before you were manager of statistics,

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1 what was your job at Abbott?

2 A. The same job, different title.

3 Q. What was the title?

4 A. Senior Statistician II, I believe.

5 Q. Roman numeral II?

6 A. That's correct.

7 Q. How long did you hold that job?

8 A. Approximately three years.

9 Q. From 2002 to 2005?

10 A. Approximately.

11 Q. What were your responsibilities as

12 Senior Statistician II?

13 A. The same as they are today.

14 Q. In the 2002 to 2005 period, did you

15 report to David Morris?

16 A. I do not recall the date that David

17 Morris stopped being my immediate supervisor. It

18 was in that time frame.

19 Q. Why did David Morris leave Abbott?

20 A. I do not know.

21 Q. What was your job at Abbott prior to

22 being Senior Statistician II?

23 A. Senior Statistician I.

24 Q. Makes sense. What was the period you

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1 held that job, ballpark?

2 A. Probably around three years prior, just

3 starting --

4 Q. So would you say --

5 A. -- before my next promotion.

6 Q. Sorry I cut you off.

7 A. Sorry.

8 Q. Finish your answer.

9 A. Approximately three years prior to my

10 promotion to Senior Stats II.

11 Q. So in the 1999 to 2002 time period?

12 A. I believe that's correct.

13 Q. And your responsibilities as Senior

14 Statistician I?

15 A. Was to help clinical teams review

16 protocols, case report forms, clinical study

17 reports, design studies, program tables for

18 analysis.

19 Q. Focusing on your responsibility as a

20 Senior Statistician I, how many people reported to

21 you?

22 A. None.

23 Q. You reported to David Morris at that

24 time, right?

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1 A. Yes.

2 Q. While you were a Senior Statistician I  
3 in the period 2000 to 2001, how many clinical  
4 trials did you work on?

5 A. I don't recall.

6 Q. Approximately?

7 A. What is the time frame? I'm sorry.

8 Q. Let's take 2000/2001.

9 A. Approximately a dozen.

10 Q. One of those was the clinical trial  
11 known as M99-114, correct?

12 A. That's correct.

13 Q. You worked on the 99-114 study during  
14 the period 2000/2001, right?

15 A. Yes.

16 Q. And during that time, you worked on  
17 approximately ten or so additional clinical  
18 trials?

19 A. Yes.

20 Q. When did you start at Abbott?

21 A. 1995.

22 Q. From '95 to '99, what were your jobs  
23 there?

24 A. I was a statistician.

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1 Q. Is that a lower title than Senior

2 Statistician I?

3 A. It was -- I'm sorry. I would have

4 been hired -- I was hired as an Associate

5 Statistician I, promoted to Senior Statistician I.

6 Q. Okay. And that promotion was in '99,

7 right?

8 A. I don't recall the exact date. I'm

9 sorry.

10 Q. Okay. Before you worked at Abbott,

11 where did you work?

12 A. Parexel International.

13 Q. Can you spell that for the record.

14 A. P-a-r-e-x-e-l.

15 Q. What did you do there?

16 A. I was a statistician.

17 Q. How long were you employed there?

18 A. Approximately three-and-a-half years.

19 Q. '92 to '95?

20 Did you have any other jobs as

21 statistician before you worked at Parexel?

22 A. No.

23 Q. Can you give me your educational

24 background, beginning with college.

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1 A. I have a Master's and Bachelor's Degree  
2 in Statistics from Brigham Young University in  
3 Provo, Utah.

4 Q. What year did you earn it?

5 A. Which degree?

6 Q. Let's start with the BA.

7 A. I'm sorry. I don't recall the -- the  
8 dates. It was a Bachelor's of Science.

9 I don't -- I'm sorry. I don't recall the year of  
10 graduation.

11 Q. I guess everybody is getting older.

12 What about the MBA?

13 A. I have a Master's of Science in MS.

14 Q. What year did you earn that?

15 A. I'm sorry. I don't recall the year  
16 that I graduated.

17 Q. How old are you?

18 A. Forty-six.

19 Q. Your Master's in Science, did you have  
20 any kind of specialty?

21 A. Statistics.

22 Q. Do you have any background in the  
23 development of pharmaceutical compounds?

24 A. Yes.

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1 Q. In connection with your work at Abbott?

2 A. Yes.

3 Q. Other than the work you do in  
4 connection with clinical trials on statistics,  
5 what work do you do at Abbott presently regarding  
6 the development of clinical trials?

7 A. Could you restate your question?

8 Q. Yeah. That's not a very good one.

9 Do you do work with respect to the  
10 development of clinical compounds other than with  
11 respect to statistics?

12 A. Again, I don't understand your  
13 question.

14 Q. Other than your work in connection with  
15 clinical trials at Abbott, do you do anything else  
16 there?

17 A. No.

18 Q. In connection with your work on  
19 clinical trials, you work with persons at Abbott  
20 on the regulatory side, fair?

21 A. Yes.

22 Q. On the commercial side, right?

23 A. Yes.

24 Q. And on the development side?

1 A. Yes. I'm in development.

2 Q. When did you begin working on the

3 M99-114 study?

4 A. I don't recall.

5 Q. What did you do with respect to the

6 M99-114 study?

7 A. Could you be more specific? I'm not

8 understanding your question.

9 Q. What were your responsibilities with

10 respect to the clinical trial known as M99-114?

11 A. Consulting with the clinical team in

12 development of the protocol, reviewing the case

13 report forms as they were developed, supervising

14 production of analysis for the final study report,

15 consulting with the clinical team ongoing as

16 patients were enrolled, and writing the clinical

17 study report at the end of the -- the trial.

18 Q. Did you also conduct analyses of the

19 data regarding patients during the study itself?

20 MR. PHILLIPS: Objection.

21 BY MR. ZWICKER:

22 Q. Let me ask you a different question.

23 A. Thank you.

24 Q. In connection with your



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1 responsibilities on 99-114, did you also analyze

2 the data from the clinical science before the

3 study was unblinded?

4 A. No.

5 Q. Did you -- did you conduct any analyses

6 of how patients were doing on the study before the

7 study was unblinded?

8 MR. PHILLIPS: Objection, vague.

9 BY THE WITNESS:

10 A. In the sense that I would use

11 "analyze," no.

12 BY MR. ZWICKER:

13 Q. What word would you use?

14 A. Summarize.

15 Q. Did you draw conclusions from the data

16 you were reviewing before the study was unblinded?

17 A. Before it was unblinded?

18 Q. Yeah.

19 A. No.

20 (WHEREUPON, a certain document was

21 marked Thomas Deposition Exhibit

22 No. 1, for identification, as of

23 4/13/07.)

24 MR. PHILLIPS: Joe, we're starting with a new

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1 technology, anything is possible, as reproducing  
2 pictures and documents.

3 Q. Mr. Thomas, you were the person that  
4 helped create the objectives for the 99-114 study,  
5 right?

6 A. No.

7 Q. You had some role in them?

8 A. Objectives? No.

9 Q. Let me read you this sentence. It  
10 says:

11 "This study is designed to enroll  
12 320 patients (80 patients in each  
13 treatment group)."

14 You see that?

15 A. I do.

16 MR. PHILLIPS: I think you left out the  
17 "approximately" before the "320."

18 MR. ZWICKER: I'll read it again.

19 BY MR. ZWICKER:

20 Q. "This study is designed to enroll  
21 approximately 320 patients (80 patients  
22 in each treatment group). This sample  
23 size will allow for the detection of a  
24 .46 effect size in the average Daily

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1 Pain Intensity score" from "change from  
2 baseline to the final evaluation  
3 between any... treatment group and  
4 placebo at .05 (two-tailed Type I error)  
5 level with at least 80 percent power."

6 Did I read that right?

7 A. No.

8 Q. How did I read it wrong?

9 A. You left a couple words out.

10 Q. Mr. Thomas, is this your understanding  
11 of the design of the M99-114 study?

12 A. No. This is not the design. This is  
13 the sample size calculation.

14 Q. But it's not just the sample size  
15 calculation. It's also the intent to achieve a  
16 .46 effect, right?

17 A. No.

18 Q. What is it?

19 A. This is the sample size used to power  
20 the study.

21 Q. What role did you have in coming up  
22 with the sample size used to power the study?

23 A. Worked with the clinical team on  
24 different scenarios and ran the calculation to

1 come up with the sample size that was based on the  
2 assumptions that were discussed with the clinical  
3 team.

4 Q. What work did you do with the clinical  
5 team to come up with the sample size?

6 A. Met with them.

7 Q. What else?

8 A. Reviewed pertinent journal articles.

9 Q. Whose decision was it to come up with a  
10 sample size of 80 patients in each treatment  
11 group?

12 A. I don't recall.

13 Q. Was it yours?

14 A. No.

15 Q. Was it David Morris'?

16 A. No.

17 Q. Whose was it?

18 A. I don't recall.

19 Q. Whose could it have been?

20 MR. PHILLIPS: Objection, calls for  
21 speculation.

22 BY MR. ZWICKER:

23 Q. Who else worked on the -- who else  
24 worked on the study?

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1 BY MR. ZWICKER:

2 Q. In your experience, does Abbott use  
3 phase 2 -- use 80 percent power in phase 2  
4 studies?

5 MR. PHILLIPS: Objection, vague.

6 BY THE WITNESS:

7 A. Sometimes. Yes and no.

8 BY MR. ZWICKER:

9 Q. Have you been involved in clinical  
10 trials where the expected power was less than  
11 80 percent?

12 A. Yes.

13 Q. Did you agree with the decision by  
14 Abbott to use 80 percent power in the 99-114  
15 study?

16 A. I believe I answered that question  
17 already. Yes.

18 Q. You did. Why did you agree?

19 A. It's standard for the industry.

20 Q. Did you believe -- did you personally  
21 believe that using 80 percent power would help  
22 99-114 move to phase 3 clinical trials?

23 A. I don't understand the connection. I'm  
24 sorry.

1 Q. When Abbott plans clinical trials, its  
2 objective is to be sure that it gets -- it can use  
3 the data from the trials, right?

4 A. That is correct.

5 Q. And with respect to this trial, did  
6 Abbott believe that an 80 percent power would  
7 allow it to use the results of this trial?

8 MR. PHILLIPS: Objection, lack of foundation;  
9 object to the form.

10 BY THE WITNESS:

11 A. I believed 80 percent power was  
12 adequate for us to conduct a study ethically and  
13 use the data.

14 BY MR. ZWICKER:

15 Q. Use the data where?

16 A. In decisions regarding the compound.

17 Q. Decisions regarding to move the  
18 compound to phase 3?

19 A. Or whatever Abbott wanted to do with  
20 the compound.

21 Q. What was your understanding of what  
22 Abbott wanted to do with the compound?

23 A. Develop the compound, file an NDA.

24 Q. And commercialize it?

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1 A. That is correct.

2 Q. So you believed that an 80 percent

3 power would assist Abbott in commercializing the

4 compound, right?

5 A. Yes.

6 MR. ZWICKER: Let's mark this as 2.

7 (WHEREUPON, said document was

8 marked Thomas Deposition Exhibit

9 No. 2, for identification, as of

10 4/13/07.)

11 BY MR. ZWICKER:

12 Q. Mr. Thomas, before you is a Summary of

13 Anticipated Expert Report by Dr. Bruce E. Rodda.

14 Do you have that?

15 A. I do.

16 Q. Have you read this before?

17 A. I don't know if I read this version.

18 I have read information from Dr. Rodda.

19 Q. In connection with this lawsuit?

20 A. Correct.

21 Q. Turn to page 6 of Dr. Rodda's report,

22 would you. There's a paragraph that begins with

23 "Organizations." Do you see that?

24 A. I do.

1 A. I was involved with the calculation of  
2 the power based on the assumptions given to us by  
3 the clinical team. Is that your question?

4 Q. How did you determine that a sample  
5 size of 80 patients per arm was needed to achieve  
6 80 percent power?

7 MR. PHILLIPS: Objection, assumes facts not  
8 in the record.

9 MR. ZWICKER: Let me -- let me restate that.

10 MR. PHILLIPS: Sure.

11 BY MR. ZWICKER:

12 Q. How did you determine the sample size  
13 needed to achieve 80 percent power?

14 MR. PHILLIPS: Object to the form.

15 BY THE WITNESS:

16 A. I'm -- I don't recall that I actually  
17 did that for this study.

18 BY MR. ZWICKER:

19 Q. When Abbott calculated the sample size,  
20 did it assume that all persons enrolled in the  
21 study would complete it?

22 A. No.

23 Q. What was the assumption made by Abbott  
24 at the planning stage regarding whether subjects



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1 enrolled in the study would have to complete it to  
2 achieve 80 percent power?

3 A. Could you repeat that, please?

4 Q. Yeah. What conclusions did Abbott draw  
5 about how many subjects enrolled in the study  
6 would have to complete it to achieve 80 percent  
7 power?

8 A. I don't believe a percentage was  
9 determined.

10 Q. Well, what discussions were had  
11 regarding the impact of any premature terminations  
12 on power at the planning stage of the study?

13 A. The calculation of the sample size in  
14 the -- in the calculation of the dropout rate  
15 is -- it's inf- -- it's inferred by the -- the  
16 results that were used to help determine the  
17 effect size that was used to calculate the sample  
18 size.

19 Q. At the planning stage of the study, did  
20 Abbott consider the impact of any dropouts on  
21 power?

22 A. Yes.

23 Q. What discussions did it have that you  
24 were involved in?

1 BY THE WITNESS:

2 A. I disagree.

3 BY MR. ZWICKER:

4 Q. You disagree with that statement?

5 A. I do.

6 Q. Okay. Would you think -- consider a

7 50 percent premature termination rate to be

8 substantial, sir?

9 MR. PHILLIPS: Objection, incom- -- strike

10 that.

11 Objection, improperly calls for opinion

12 testimony, vague.

13 BY THE WITNESS:

14 A. No.

15 BY MR. ZWICKER:

16 Q. You think that's appropriate?

17 MR. PHILLIPS: Same objections.

18 BY THE WITNESS:

19 A. In some studies, yes.

20 BY MR. ZWICKER:

21 Q. In the 99-114 study, was that an

22 appropriate rate of premature termination, sir?

23 A. I don't recall.

24 MR. PHILLIPS: Objection.

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1 (WHEREUPON, said document was

2 marked Thomas Deposition Exhibit

3 No. 5, for identification, as of

4 4/13/07.)

5 MR. ZWICKER: The record should reflect that

6 before the witness is a Clinical Protocol for the

7 99-114 study, and it's marked as Exhibit 5.

8 BY MR. ZWICKER:

9 Q. Mr. Thomas, you recognize this

10 document?

11 A. Yes.

12 Q. In fact, you signed for David Morris on

13 it, didn't you?

14 A. I did.

15 Q. What role did you have in creating this

16 protocol for the 99-114 study?

17 A. I worked in conjunction with the

18 clinical team in reviewing the -- the document.

19 Q. Were you satisfied with the accuracy of

20 the protocol --

21 A. I was.

22 Q. -- based on your work?

23 MR. PHILLIPS: Mr. Thomas, please remember to

24 wait -- wait until Mr. Zwicker completes his

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1 Q. Okay. And an intent-to-treat subject  
2 is someone who prematurely terminates, right?

3 MR. PHILLIPS: Objection, mischaracterizes  
4 the testimony.

5 BY THE WITNESS:

6 A. No.

7 BY MR. ZWICKER:

8 Q. An intent-to-treat subject is someone  
9 who receives at least one dose of the study drug?

10 A. According to the definition in this  
11 protocol, an intent-to-treat is, they had to  
12 receive at least one dose of study drug at the  
13 baseline diary assessment and at least one  
14 post-dose diary assessment. All the completers  
15 would, therefore, then be intent-to-treat.

16 Q. Would you agree with me that there's a  
17 difference between someone who prematurely  
18 terminates a study and someone who completes it?

19 MR. PHILLIPS: Objection, vague; objection,  
20 calls for improper opinion testimony.

21 BY THE WITNESS:

22 A. I'm not sure what your question is.  
23 I'm sorry.

24 BY MR. ZWICKER:

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1 Q. In your mind, is there a distinction  
2 regarding the meaningfulness of the data between a  
3 person who completes the study and a person who  
4 doesn't?

5 MR. PHILLIPS: Objection, vague, incomplete  
6 hypothetical.

7 BY THE WITNESS:

8 A. The data are not the -- necessarily the  
9 same. They are both useful.

10 BY MR. ZWICKER:

11 Q. Okay. Are they equally useful?

12 MR. PHILLIPS: Objection to the form.

13 BY MR. ZWICKER:

14 Q. Let me ask you a different question.

15 For purposes of the 99-114 study, is  
16 your view that the data for those two groups is  
17 equally useful?

18 MR. PHILLIPS: Objection, vague.

19 BY THE WITNESS:

20 A. I'm sorry. I -- your question is  
21 vague. I don't understand exactly what data we're  
22 talking about. All data?

23 BY MR. ZWICKER:

24 Q. The data that was collected from the

1 study.

2 A. Data from both groups is useful.

3 Q. What would you rather have, Mr. Thomas,  
4 a patient who completed the study or a patient who  
5 prematurely terminated?

6 MR. PHILLIPS: Objection, incomplete  
7 hypothetical.

8 BY MR. ZWICKER:

9 Q. And by "the study," I mean the 99-114  
10 study.

11 A. In general, I prefer all patients to  
12 complete the study.

13 Q. Why?

14 A. They bring more data, and it also shows  
15 that the study was -- the drug would be tolerable.

16 Q. And so the more patients that  
17 prematurely terminate for adverse events, the more  
18 likely you are to conclude that the drug isn't  
19 being tolerated, true?

20 MR. PHILLIPS: Objection, lack of foundation.

21 BY THE WITNESS:

22 A. Can you repeat your question?

23 BY MR. ZWICKER:

24 Q. And so the more patients that

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1 prematurely terminate the study for adverse  
2 events, the more likely you are to conclude that  
3 the drug isn't being tolerated, right?

4 A. Yes.

5 MR. PHILLIPS: Counsel, when we get a chance,  
6 we have been going about an hour and fifteen  
7 minutes, I believe. If we could take a break?

8 MR. ZWICKER: Yes. Let's do it now.

9 MR. PHILLIPS: Okay.

10 THE VIDEOGRAPHER: Going off the video record  
11 at 9:17 a.m.

12 (WHEREUPON, a recess was had from  
13 9:17 a.m. until 9:24 a.m.)

14 THE VIDEOGRAPHER: And we are back on the  
15 video record at 9:24 a.m. This is Tape 2.

16 (WHEREUPON, a certain document was  
17 marked Thomas Deposition Exhibit  
18 No. 6, for identification, as of  
19 4/13/07.)

20 MR. ZWICKER: The record should reflect that  
21 before the witness is Thomas Exhibit No. 6, which  
22 is an e-mail and enclosure from Marilyn Collicott  
23 dated August 9th, 2000.

24 BY MR. ZWICKER:

Thomas, James (Linked) 04/13/2007 8:05:00 AM

1 A. Yili Pritchett.

2 Q. What did you tell her?

3 A. I needed to be off a couple days to --  
4 for deposition.

5 Q. Mr. Thomas, do you remember being asked  
6 to recalculate power calculations in the year 2000  
7 in light of the enrollment challenges to the  
8 99-114 study?

9 A. I don't being -- I don't recall being  
10 asked to do that.

11 Q. Do you recall doing any work with  
12 respect to the power calculations after the study  
13 began enrolling patients?

14 A. Yes.

15 Q. What work did you do?

16 A. Looked at various scenarios of what the  
17 power would be with a smaller number of patients  
18 than planned.

19 Q. Why did you do that?

20 A. It would have been at someone's  
21 request. I don't recall who.

22 Q. In your own mind, did you believe you  
23 were being asked to perform those calculations  
24 because Abbott was not reaching its enrollment



Thomas, James (Linked) 04/13/2007 8:05:00 AM

1 rate, however, will result in less than  
2 80 percent power even if we were to  
3 reach our enrollment goal."

4 You see that?

5 A. I do.

6 Q. What do you understand that to mean?

7 MR. PHILLIPS: Objection, lack of foundation,  
8 calls for speculation.

9 BY THE WITNESS:

10 A. This appears to be a draft letter.  
11 I do not know if this letter was ever sent to  
12 anyone. I don't know if this letter was ever  
13 reviewed. I don't understand what this sentence  
14 is actually trying to put forward.

15 BY MR. ZWICKER:

16 Q. Do you agree with the proposition that  
17 a premature termination rate with respect to the  
18 99-114 study will result in less than 80 percent  
19 power even if the enrollment goal was reached?

20 MR. PHILLIPS: Objection, lack of foundation.

21 BY MR. ZWICKER:

22 Q. Do you agree with that statement?

23 A. No.

24 Q. Why not?

1 A. Because termination -- a termination  
2 rate was already built into the power  
3 calculations. This study was assumed to have  
4 dropouts.

5 Q. How many?

6 A. I don't recall.

7 Q. Where would it have been written?

8 A. It would not have been written, to my  
9 knowledge. It's --

10 Q. Would it have been in the protocol?

11 A. It's in -- it's in -- used in the  
12 calculation of the effect size that was used in  
13 determining the sample size that was calculated  
14 for the study.

15 Q. Would it have been in the protocol?

16 A. The effect size is in the protocol.

17 Q. No. Would the -- would the rate of  
18 premature terminations been in the protocol?

19 A. It's in the effect size.

20 Q. But it's not stated anywhere in the  
21 protocol, the number of premature terminations  
22 that you can -- you would have anticipated?

23 MR. PHILLIPS: Objection. The document  
24 speaks for itself, lack of foundation.

Thomas, James (Linked) 04/13/2007 8:05:00 AM

1 you ever could make that determination.

2 Q. In your own mind on December 14th,  
3 2000, do you have any doubts about the usefulness  
4 of the study in light of the fact that planned  
5 power won't be achieved?

6 MR. PHILLIPS: Are you asking what he --

7 MR. ZWICKER: As of December 14th, 2000.

8 MR. PHILLIPS: Objection, assumes facts not  
9 in the record.

10 BY THE WITNESS:

11 A. Would you read back your question,  
12 please.

13 BY MR. ZWICKER:

14 Q. In your own mind, on December 14th,  
15 2000, did you have any doubts about the usefulness  
16 of the study in light of the fact that planned  
17 power would not be achieved?

18 A. No.

19 Q. None?

20 A. No.

21 Q. So your testimony is that on  
22 December 14th, 2000, you viewed the failure to  
23 achieve planned power as not relevant to the  
24 study?

Thomas, James (Linked) 04/13/2007 8:05:00 AM

1 A. I don't recall. I would need to look  
2 at the analysis tables.

3 BY MR. ZWICKER:

4 Q. Mr. Thomas, do you recall at the  
5 titration meetings that you attended whether  
6 Abbott was considering new trials for 594 to  
7 address tolerability through different titration  
8 schemes?

9 MR. PHILLIPS: Objection, vague as to time.

10 BY THE WITNESS:

11 A. I --

12 BY MR. ZWICKER:

13 Q. Let me say in the 2001 -- around the  
14 January 2001 time period.

15 A. I don't recall the time period; but at  
16 some point either during or after the 114 study,  
17 discussions -- there were discussions concerning  
18 alternate titration schemes than what was used in  
19 the 114 study.

20 Q. And that would have required additional  
21 clinical trials, right?

22 A. That is correct.

23 Q. Before the data was unblinded,

24 Mr. Thomas, did you come to the conclusion that

Thomas, James (Linked) 04/13/2007 8:05:00 AM

1 the results of the ABT -- of the 99-114 study were  
2 going to be used to develop follow-on compounds  
3 rather than 594?

4 A. Could you -- could you read that back.  
5 I'm sorry.

6 Q. Before the results were unblinded for  
7 the 99-114 study -- can you have that period in  
8 mind?

9 A. Okay.

10 Q. (Continuing) -- did you form the  
11 conclusion that the results of the 99-114 study  
12 would be used not for the commercialization of 594  
13 but for the development of a follow-on compound  
14 for 594?

15 A. No.

16 Q. Do you know if anybody else had that  
17 view?

18 A. I don't know other people's views.

19 Q. I'm just asking if anybody expressed  
20 that view to you.

21 A. No one expressed that view to me.

22 Q. Do you read Exhibit 23, Mr. Thomas, to  
23 contemplate the undertaking of additional clinical  
24 trials for 594 with different titration schemes?

Thomas, James (Linked) 04/13/2007 8:05:00 AM

1 A. I didn't actually prepare any  
2 presentations. I'm sorry. That -- I thought you  
3 asked if I had helped in the preparation. Is that  
4 not correct?

5 Could you read the question back.

6 Q. I'll ask you the question again.

7 A. I'm sorry.

8 Q. Did you have any role in preparing  
9 presentations to Abbott management regarding the  
10 results of the 99-114 study?

11 A. Yes.

12 Q. What presentations did you prepare?

13 A. I didn't actually prepare any  
14 presentations. I prepared data -- all that --  
15 I prepared all of the data for the 594 study that  
16 was analyzed, and that data was used in  
17 presentations.

18 Q. So you evaluated the unblinded data?

19 A. Yes.

20 Q. Is that fair?

21 A. That is -- that is my role as a  
22 statistician, to -- to run the analysis on the  
23 unblinded data.

24 Q. What analyses did you run?

Thomas, James (Linked) 04/13/2007 8:05:00 AM

1 A. Would you like me to go through as much  
2 as I can remember?

3 Q. Go through what you can remember.

4 A. Okay. Typically, we start by looking  
5 at the number of patients enrolled at each site.  
6 We break that down by treatment group. We look  
7 then, generally, at the demographics variables:  
8 Gender, age, weight, race, height, ethnicity. We  
9 look at concomitant medication use. We look at  
10 exposure, how long they were on drug.

11 We look at the disposition; how many  
12 people prematurely discontinued, for what reasons,  
13 overall, over time. We look at -- we often look  
14 at the discontinuations over time and in totality.

15 There were various efficacy measures in  
16 this study -- I don't recall them all -- that it  
17 was the primary, which was the diary-based pain  
18 assessments. I believe there was a site-based  
19 pain assessment, a global assessment of study  
20 drug, SF 36. I don't recall if the study had the  
21 neuropathic pain scale.

22 Then we also look at adverse event  
23 rates overall. We look at prevalence -- often  
24 look at prevalence incidents. I don't recall if

Thomas, James (Linked) 04/13/2007 8:05:00 AM

1 we did that in this study. We look at the rel- --  
2 the severity of adverse events, the relationship  
3 to the study drug of adverse events. We look at  
4 serious adverse events, deaths, adverse events  
5 leading to premature discontinuation, hematology,  
6 chemistry and urinalysis, mean change from  
7 baseline, shift tables, vital signs mean change  
8 from baseline to min/max final, sometimes shift  
9 tables, I don't recall.

10 We look at laboratory and vital signs  
11 that may meet criteria developed prior to blind  
12 break of potentially clinically sig- --  
13 clinically -- potentially clinically significance.

14 That's usually the standard analysis  
15 that we produce.

16 Q. And do you draw conclusions regarding  
17 whether or not an adverse event is statistically  
18 significant to a specific dose level?

19 MR. PHILLIPS: Objection, vague.

20 BY THE WITNESS:

21 A. I'm not sure what you mean. I'm sorry.

22 BY MR. ZWICKER:

23 Q. Well, for example, take the 150 mcg  
24 dose level.



1 Q. It's your testimony that planned power

2 doesn't change even if persons preterminate,

3 correct?

4 MR. PHILLIPS: Same objection.

5 BY THE WITNESS:

6 A. I can't speak for all cases; but in the

7 case for this study, the power calculations were

8 based on the effect size, which takes premature

9 discontinuations into account.

10 BY MR. ZWICKER:

11 Q. If you multiply 56 times four, you get

12 224, right?

13 A. I believe so.

14 Q. That's the first thing we've agreed on

15 all day.

16 A. I'm not good at math.

17 Q. The number of persons that were

18 enrolled in the study was 266?

19 A. That's what this slide purports.

20 Q. Why is there a difference between the

21 persons enrolled and the persons in the group for

22 purposes of power calculation?

23 MR. PHILLIPS: Objection, lack of foundation.

24 BY THE WITNESS:

**Thomas Exhibit 1**

**D's Exhibit IT**

James W Thomas

12/21/99 08:06 AM

To: Fred W Siebert/LAKE/PPRD/ABBOTT@ABBOTT, Kevin J Heuser/LAKE/PPRD/ABBOTT@ABBOTT  
cc: (bcc: James W Thomas/LAKE/PPRD/ABBOTT)  
Subject: 114 Sample Size

Below is my attempt at writing up the sample size section of the 114 protocol.

This study is designed to enroll approximately 320 patients (80 patients in each treatment group). This sample size will allow for the detection of a 0.46 effect size in the average Daily Pain Intensity score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation is based on results obtained from ABT-594 study M99-833 and published data using Gabapentin for patients with painful diabetic polyneuropathy (add reference here to Dec 1998 JAMA article) and assuming an 39% and 25% improvement from baseline for ABT-594 and placebo respectively.

Jim

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Thomas DEP. EX. NO. 1  
FOR ID., AS OF 4/13/07 Rmr

# **Thomas Exhibit 5**

## **D's Exhibit 534**


### **Part 1**

**ABBOTT LABORATORIES**  
**Clinical Protocol**

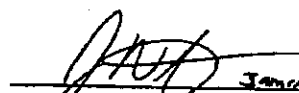
**A Randomized, Double Blind, Placebo-Controlled, Comparison  
of the Safety and Efficacy of ABT-594 to Placebo in Subjects  
with Painful Diabetic Polyneuropathy**

**Protocol M99-114**


**February 8, 2000**

  
Fred Siebert, MT-BB (ASCP)  
Senior Clinical Research Associate, Analgesia Venture

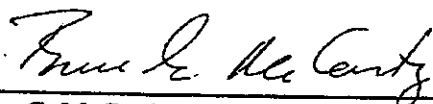
2/10/2000  
Date

  
David Morris, Ph.D.  
Manager, Clinical Statistics

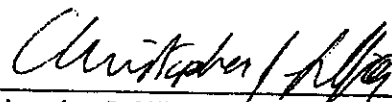
2-11-00  
Date

  
Walid Awni, Ph.D.  
Manager, Clinical Pharmacokinetics

2/11/00  
Date

  
Bruce G. McCarthy, M.D.  
Associate Medical Director, Analgesia Venture



2/10/00  
Date

  
Christopher J. Silber, M.D.  
Venture Head, Analgesia Venture

2/10/00  
Date

 **Abbott Laboratories**

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ABT-594  
Protocol M99-114  
February 8, 2000

i

## 1.0 Title Page

*Abbott Laboratories*  
Analgesia Venture, D48Q  
Clinical Study

**A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety  
and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic  
Polyneuropathy**

*ABT-594/M99-114*  
*February 8, 2000*

Development Phase: II

Investigators: Multicenter Trial

Estimated Date of First Subject to be Dosed: April 2000

Estimated Date of Last Subject to Complete Dosing: November 2000

Sponsor/Emergency Contact: Christopher J. Silber, M.D.  
Venture Head,  
Analgesia Venture  
Phone: (847) 938-5236, Fax: (847) 938-5258  
Department 48Q, Building AP34  
200 Abbott Park Road  
Abbott Park, Illinois 60064-6193

This study will be conducted in compliance with Good Clinical Practice, including  
the archiving of essential documents.

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Protocol M99-114  
February 8, 2000

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## 2.0 Study Synopsis

<b>Name of Company:</b> Abbott Laboratories  <b>Name of Finished Product:</b> ABT-594 Hard Gelatin Capsule (HGC)  <b>Name of Active Ingredient:</b> ABT-594	<b>Individual Study Table Referring to Part of the Dossier:</b> Not Applicable (N/A)  <b>Volume:</b> N/A  <b>Page:</b> N/A	<i>(For National Authority Use Only)</i>
<b>Title of Study:</b>  A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy		
<b>Investigator(s):</b> Multicenter Study		
<b>Study Center(s):</b> 30		
<b>Publication (reference):</b> N/A		
<b>Study Period (years):</b>  <b>Estimated Date of First Subject to be Dosed:</b> April, 2000  <b>Estimated Date of Last Subject to Complete Dosing:</b> November, 2000		<b>Phase of Development:</b> II
<b>Objectives:</b>  The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy, have an average of $\geq 4$ points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and have $\geq 4$ points on the site-based Pain Rating Scale (11-Point Likert) at the Baseline Visit.		
<b>Methodology:</b>  This is a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. Approximately 320 subjects will be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg, or placebo BID for 49 days on an outpatient basis. Approximately 30 sites will be recruited in order to enroll 320 subjects who meet entry criteria for this study.  Prior to any study-specific procedures at the Screening Visit, an informed consent will be signed and study eligibility determined.		

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February 8, 2000

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#### Methodology: (Continued)

Prior to study drug administration, subjects will have discontinued all analgesic medications (at least 7 days prior to the Baseline Pain Assessment Phase) and have completed the 7-day Baseline Pain Assessment Phase. Following the Baseline Pain Assessment Phase, subjects who meet entry criteria, will be randomized to a dose of study medication for 49 days (Primer and Treatment Phases). During the Treatment Phase, subjects will return to the site for Treatment Visits I, II, III and IV (Days 14, 21, 35 and 49, respectively). During the Primer and Treatment Phases, subjects will be allowed to take up to 3 grams of acetaminophen per day or up to 6 grams of acetaminophen per week (but will not be allowed to take acetaminophen within 24 hours prior to a Treatment Visit). Subjects will complete diary-based assessments of their diabetic polyneuropathy pain each day from the 7 days prior to study drug administration (Baseline Pain Assessment Phase) through Day 49 of study drug administration. In addition, subjects will undergo site-based assessments of their neuropathy pain at the Baseline Visit and Treatment Visits I, II, III and IV. Subjects will discontinue study drug administration after Treatment Visit IV and return to the site for the Follow-Up visit 7-10 days later. See Figure 9.1a, Study Schematic, for additional study layout information.

Efficacy and safety assessments will include: the Pain Rating Scale (11-Point Likert), the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), and Subject and Clinician Global Impression of Change.

No. of Subjects: 320

#### Diagnosis and Main Criteria for Inclusion:

A subject may be randomized in this study provided that he/she meets all of the Inclusion Criteria outlined below and does not meet any of the Exclusion Criteria in Section 9.3.2.

- Prior to any study specific procedure, voluntary written informed consent must be obtained from the subject after the purpose and nature of the study have been explained.
- The subject must be age 18 or older and in relatively good health with a recent stable medical history.
- The subject's weight must be  $\leq$  265 pounds.
- A female subject must be non-lactating and:
  - of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation),
  - OR
  - of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and must continue contraceptive method through the course of the study).

All female subjects must have a negative  $\beta$  subunit human chorionic gonadotropin ( $\beta$ -hCG) at the Baseline Visit. Female subjects of childbearing potential must have a negative  $\beta$ -hCG at all Treatment Visits.

- The subject must have a diagnosis of diabetes mellitus (Type I or Type II) and a diagnosis of distal symmetric diabetic polyneuropathy.
- The subject must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.

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- The location and quality of the pain under study are consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
- The subject has distal symmetric diabetic polyneuropathy symptoms (including pain) which have been stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
- The subject must have an average of  $\geq 4$  points on the diary-based Pain Rating Scale (11-Point Likert Scale) everyday during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and  $\geq 4$  points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit.

**Test Product(s):** ABT-594 75  $\mu$ g HGC (Formulation A-2)

**Dose:** ABT-594 150  $\mu$ g, 225  $\mu$ g, or 300  $\mu$ g BID (Section 9.4)

**Mode of Administration:** Oral

**Batch Number:**

Study Drug	Drug Product Lot Number
ABT-594 75 $\mu$ g HGC	58-293-AR

**Duration of Treatment:** 49 days

**Reference Therapy:** Placebo for ABT-594 HGC No. 1 Light Gray Opaque (Starch)

**Dose:** Placebo to match test product (see Section 9.4)

**Mode of Administration:** Oral

**Batch Number:**

Study Drug	Drug Product Lot Number
Placebo for ABT-594 HGC	55-243-AR-01

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**Criteria for Evaluations:**

**Efficacy:**

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. Additionally, change from baseline to each scheduled evaluation will be analyzed in a similar manner. The baseline pain score for the diary data is defined as the average of the last 7 pain scores prior to Day 1 of the study.

Change from baseline to final and each evaluation will be calculated for each of the following secondary efficacy variables:

- Site-Based Pain Rating Scale (11-Point Likert)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health] PCS, and MCS.

The efficacy evaluations recorded at the Baseline Visit will be used as the baseline score for efficacy evaluations assessed at the investigative site.

**Safety:**

Safety will be assessed by medical history, physical exam, vital signs, electrocardiogram (ECG), clinical laboratory testing, and adverse event monitoring.

**Pharmacokinetics:**

Blood samples for ABT-594 plasma assay will be taken from all subjects at Treatment Visits I and IV. For the subset of subjects who undergo intensive pharmacokinetic sampling at Treatment Visits I and IV, values of AUC,  $C_{max}$ , and  $C_{trough}$  will be determined.

**Statistical Methods:**

For all safety and efficacy analyses, the primary comparisons will be between each ABT-594 dose and placebo.

Demographic and other baseline characteristic variables will be analyzed to assess the comparability of the treatment groups.

The primary and secondary efficacy variables, including change from baseline diary and site based rating will be analyzed by using appropriate parametric and nonparametric methods. The final global evaluation scores, (Subject and Clinician) will be compared using Cochran-Mantel-Haenszel methodology.

Dose response for ABT-594 will be explored, with and without placebo included. Other efficacy analyses will be performed as appropriate.

Treatment emergent adverse events will be summarized by body system and COSTART term and compared using Fisher's exact test.

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**Statistical Methods: (Continued)**

Mean change from baseline to minimum, maximum and final values will be summarized for clinical laboratory, vital sign and ECG data. Additionally, clinical laboratory data identified as below or above limits will be flagged in the data listings. Furthermore, laboratory results which satisfy the criteria for limits for statistical analysis will be identified.

To assess dose proportionally and time invariance (from Visit I to Visit IV), dose-normalized  $C_{\text{trough}}$  and log-transformed dose-normalized AUC, and  $C_{\text{max}}$  from the subset of subject participating in intensive pharmacokinetic sampling will be subjected to a mixed effects model analysis with effects for dose level, visit, relevant covariates, and perhaps study center. The logarithmic transformation will be employed for AUC and  $C_{\text{max}}$ . An exploratory analysis will also be performed on the data set obtained from all subjects.

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ABT-594  
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#### **4.0 List of Abbreviations and Definitions of Terms**

ABT-594	[(R)-5-(2-azetidinylmethoxy)-2-chloropyridine] or A-165594
CSI	Clinical Supplies Invoice
HGC	Hard Gelatin Capsules
IVRS	Interactive Voice Response System
nAChRs	Neuronal nicotinic acetylcholine receptors
NPRO	New Product Research Order
NPS	Neuropathic Pain Scale

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## **5.0 Ethics**

### **5.1 Institutional Review Board or Independent Ethics Committee**

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human subjects in research. The investigator will obtain a duly constituted IRB/IEC review and approval of the protocol, informed consent form and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects). Abbott Laboratories will receive documentation of the study approval, the signed signature page from the study protocol, a signed Abbott Financial Disclosure form, subject informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals are anticipated since the study should be completed within one year. A complete list of documents required prior to initiation of the study is located in Appendix A.

### **5.2 Ethical Conduct of the Study**

The study will be conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version, Appendix B) and all applicable local regulations. The investigator must assure that the study will be conducted in accordance with prevailing local laws and customs or comply with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in Appendix C.

### **5.3 Subject Information and Consent**

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement will be reviewed and

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signed and dated by the subject and the person who administered the informed consent. A copy of the informed consent form will be given to the subject and a copy will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Elements of an Informed Consent are specified in Appendix D.

#### 5.4 Subject Confidentiality

All reports and communications relating to subjects in the study will identify each subject only by the subject's initials (first, middle, last) and by the subject's randomization number. Case report forms (CRF) will be used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the subject's medical records pertinent to the study will be reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to assure adequate source documentation, accuracy, and completeness of the CRFs.

The site will collect information on the subject per International Council on Harmonization (ICH) requirements, including subject name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency should also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site according to the record retention guidelines outlined in Section 12.0.

Neither the subject, the subject's physician, nor the investigator will be informed of the subject's pharmacogenetic results, should they be obtained. If performed, results from individual subjects will be kept confidential and will not be given to anyone not directly involved with this research study. The deoxyribonucleic acid (DNA) samples will be stored by Abbott Laboratories in a secure storage space with adequate measures to protect confidentiality. The DNA samples will be kept by Abbott Laboratories until destroyed by Abbott when this research is completed or the required sample retention time has been satisfied.

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## **6.0 Investigators and Study Administrative Structure**

### **6.1 Investigative Sites**

Investigative sites will be selected by Abbott Laboratories. Approximately 30 sites will be selected to enroll subjects for this study.

### **6.2 Sponsor Information**

The sponsor, Abbott Laboratories, will coordinate the activities for initiating this clinical study. The protocol, CRFs and sample informed consent form will be generated by Abbott Laboratories. The database for this study will be created using NOMAD®, a data management system. Designated statisticians at Abbott Laboratories will be responsible for the statistical analysis of the data.

### **6.3 Contract Research Organization**

Abbott Laboratories will delegate prestudy (if necessary) and initiation visits, site monitoring, and post-study site visits to a Contract Research Organization (CRO) for the conduct of this clinical study. The sponsor and CRO will maintain contact in order to manage adequately the progress of the study. The CRO will coordinate and perform all site visits and will prepare trip reports, using the Abbott format, for each visit performed. These reports will detail the activities conducted at all investigative sites and will include all relevant observations. All trip reports will be forwarded to the sponsor in a timely manner to ensure appropriate site management, adhering to Abbott Laboratories Standard Operating Procedures (SOP).

### **6.4 Clinical Supply Management**

Clinical supplies will be prepared by Abbott Laboratories (Investigational Drug Services, D-492) for the study and sent to all investigational sites. Abbott Laboratories will authorize the release of clinical supplies once the appropriate essential documents have been received from the respective site and upon approval by Abbott Laboratories Regulatory Affairs.

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All subjects will be centrally randomized by site and assigned to a treatment group (using a randomization supplied by Abbott Laboratories) using an Interactive Voice Response System (IVRS). The IVRS will be contracted from:

ClinPhone Inc.  
29 Emmons Drive, C40  
Princeton, NJ 08540

Blinded study medication for each randomized subject (using a randomization supplied by Abbott Laboratories) will also be assigned using IVRS. Each site will keep an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records (Appendix E), and records for return of used and unused clinical supplies to Abbott Laboratories. Clinical Research Associates (CRAs) will check drug accountability records regularly.

## **6.5 Central Laboratory**

This study will utilize one central laboratory contracted by, and under the direction of, Abbott Laboratories. All protocol specified clinical laboratory tests will be performed by the following central laboratory:

Covance Central Laboratory Services  
8211 SciCor Drive  
Indianapolis, IN 46214

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## 6.6 Administrative Structure

The administrative structure for this study is depicted in Figure 6.6a.

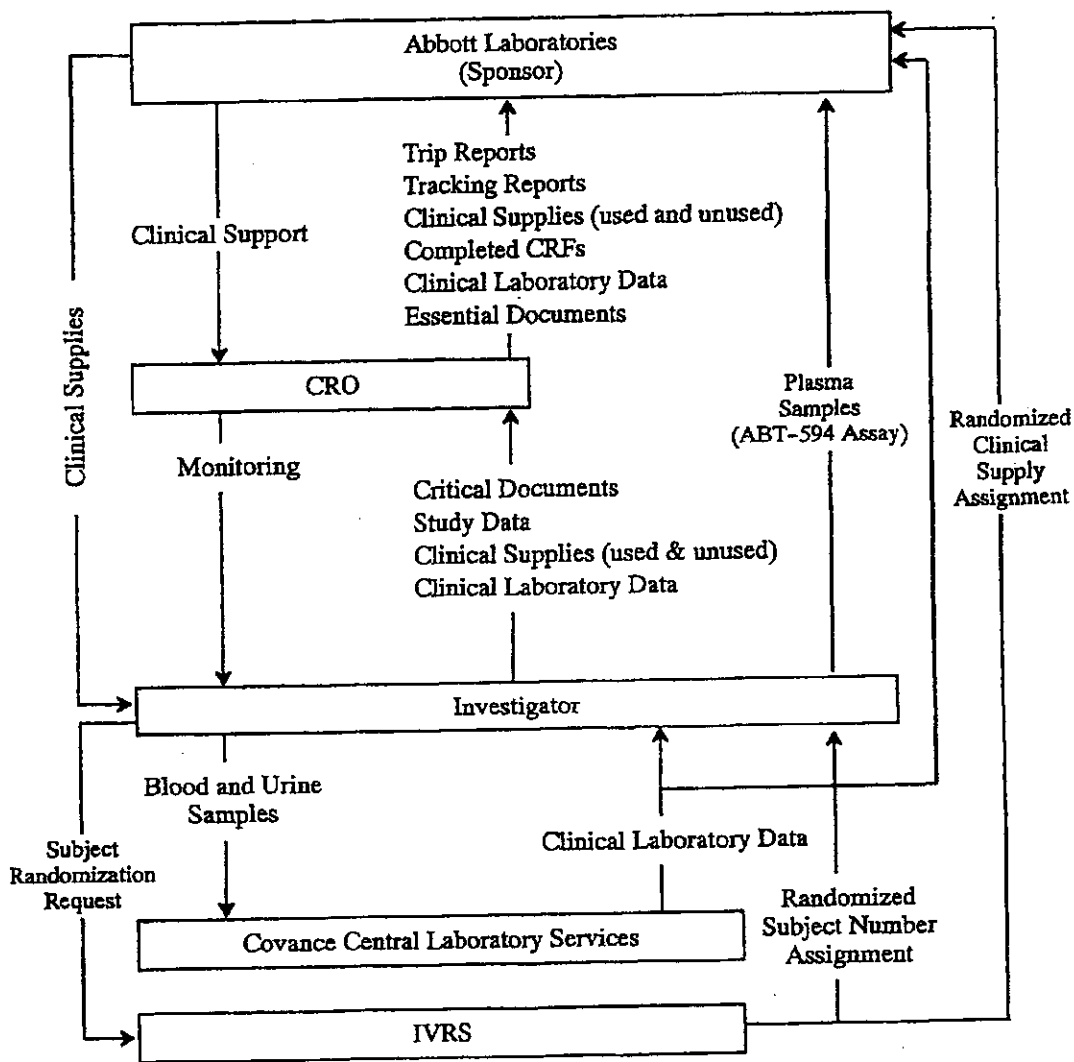


Figure 6.6a Administrative Structure

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## 7.0 Introduction

### 7.1 Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.<sup>1</sup>

Currently there are four major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs/COX-2 inhibitors), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants [TCAs]), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. COX-2 inhibitors may improve on this gastrointestinal profile, but other adverse events may become evident. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in subjects receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of an analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

### 7.2 ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (+)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than morphine in rodent models of antinociception.<sup>2</sup> The antinociceptive effects of (+)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (+)-epibatidine appears to be a potent antinociceptive agent that

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acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (+)-epibatidine is quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.<sup>3</sup> Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is a novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 in pre-clinical studies did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

In pre-clinical studies, ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.



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Human clinical trials with ABT-594 began in 1997. Initial clinical trials were conducted using oral solution formulations. Subsequently, a soft elastic capsule (SEC) formulation and, later, a hard gelatin capsule (HGC) formulation were developed and used in clinical trials.

Phase I clinical trials of the oral solution formulations suggested that 150 µg/day would be the maximally tolerated dose. Subsequent experience in Phase I and II trials with the solid formulations (SEC and HGC), however, has suggested that higher doses would be tolerated. Two Phase I studies with the HGC formulation have recently been completed: Study M99-076 ("A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Pharmacokinetics of Ascending Doses of Twice Daily Dosing Regimens of a Hard Gelatin Capsule Formulation of ABT-594 in Healthy Adult Subjects") and M99-120 ("A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability and Pharmacokinetics of Escalating Doses of Twice Daily Dosing of a Hard Gelatin Capsule Formulation of ABT-594 in Adult Subjects in General Good Health"). Study M99-076 demonstrated that the ABT-594 HGC formulation was generally well tolerated at fixed (untitrated) doses up through 300 µg BID for 14 days. Study M99-120 included titrated doses up through 450 µg BID for 5 days. Adverse events, significantly different than placebo, for subjects receiving 300 µg BID for 14 days in Study M99-076 included: dizziness, nausea, vomiting, asthenia and diarrhea (all of which were considered to be mild in the opinion of the investigator). In addition, results from Study M99-120 suggested that a short period of dose escalation at the initiation of therapy improved tolerability. Throughout Phase I studies of ABT-594, subjects generally tolerated ABT-594 better when dosing followed a meal and after 3-4 days of repeated dosing (the period in which most adverse events occur).

Phase II has included (to date) efficacy and safety studies of ABT-594 in molar extraction, osteoarthritis and neuropathic pain. Based upon a study of molar extraction pain (Study M97-772, "A Randomized, Double-Blind, Single Dose Comparison of an Oral Solution of ABT-594, Ibuprofen, and Placebo in a Post-Surgical Dental Pain Model"), 100 µg ABT-594 (single dose oral solution) appeared to be a minimally efficacious dose in acute pain.

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A study of ABT-594 in osteoarthritis (Study M98-826, "A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 and Ibuprofen to Placebo in Patients with Pain Associated with Osteoarthritis of the Knee") evaluated the ABT-594 SEC formulation at doses of 25, 50 and 75 µg BID for 3 weeks and a study of ABT-594 in neuropathic pain (Study M98-833, "A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Patients with Painful Polyneuropathies") evaluated the same formulation at doses of 25 and 75 µg BID for 3 weeks. Both studies suggested a trend towards analgesic effect at 75 µg BID. In addition, 75 µg BID was generally well tolerated. The most common adverse events (greater than or equal to 5%) for subjects receiving 75 µg BID ABT-594 in the osteoarthritis and neuropathic pain studies (combined) were nausea (15%), headache (13%), dizziness (7%), insomnia (6%) and vomiting (5%). ABT-594 appeared to be tolerated better after the first week of therapy (an effect not related to premature terminations).

Data from Phase I and II studies completed to date suggest that ABT-594 will be generally well tolerated at doses higher than previously studied in Phase II trials (higher than 75 µg BID). In addition, data from Phase II trials suggest that, because a trend toward analgesic efficacy was seen at 75 µg BID, a study of higher doses may demonstrate greater analgesic efficacy. The current study, therefore, will be performed to test this hypothesis.

## 8.0 Study Objectives

The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy, have an average of  $\geq 4$  points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and have  $\geq 4$  points on the site-based Pain Rating Scale (11-Point Likert) at the Baseline Visit.

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## 9.0 Investigational Plan

### 9.1 Overall Study Design and Plan: Description

This is a Phase II, randomized, double blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. Approximately 320 subjects will be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg or placebo BID for 49 days on an outpatient basis. Approximately 30 sites will be recruited in order to enroll approximately 320 subjects who meet entry criteria for this study.

The study will be divided into 5 phases: Screening Phase (Day -22 to Day -8), Baseline Pain Assessment Phase (Day -7 to Day -1), Primer Phase (Day 1 to Day 7), Treatment Phase (Day 8 to Day 49) and Post-Treatment Phase (Day 50 to Day 59). Day 1 is the first day of study drug administration. Subjects will be allowed a window of  $\pm 3$  days for each study visit. The study design is depicted in Figure 9.1a.

Subjects will review and sign the informed consent prior to the conduct of any study specific procedures. Subjects will then be screened for eligibility by medical history, physical examination, vital sign measurements, and clinical laboratory tests. Those subjects taking tricyclics, serotonin-specific reuptake inhibitors (SSRIs), antiepileptic drugs (AEDs), or other analgesics for the treatment of their pain must have discontinued these drugs at least 7 days prior to the Baseline Pain Assessment Phase (Day -7 to Day -1). During the Baseline Pain Assessment Phase, subjects will complete, at approximately 11 AM each morning, the diary-based Pain Rating Scale (11-Point Likert Scale) of their diabetic polyneuropathy pain intensity. Subjects will not be permitted to take concomitant analgesics, except for limited doses of acetaminophen (as specified in Section 9.4.7) during the Baseline Pain Assessment Phase.

On the day after the Baseline Pain Assessment Phase, subjects will return to the site for their Baseline Visit (Day 1). At this visit, diaries will be collected and reviewed. In addition, subjects will complete the site-based Pain Rating Scale (11-Point Likert Scale). Subjects who meet all entry criteria, including an average of  $\geq 4$  points on the

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diary-based Pain Rating Scale (11-Point Likert) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and  $\geq 4$  points on the site-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Visit, will then complete the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute). Subjects will undergo an interim medical history, physical examination, vital sign measurements, ECG and clinical laboratory tests.

Subjects who meet all entry criteria at the Baseline Visit will be randomly assigned in an equal ratio into 1 of 4 treatment groups: ABT-594 150 µg BID, ABT-594 225 µg BID, ABT-594 300 µg BID, or placebo. Subjects will start study drug at the evening dose on Day 1 (as specified in Section 9.4.5). During the Primer Phase, subjects randomized to ABT-594 will receive a fixed dose escalation of ABT-594 (as specified in Section 9.4.1). Following the Primer Phase, subjects will enter the Treatment Phase (Day 8) and will continue their treatment for a total of 49 days. During the Primer and Treatment Phases, subjects will not be permitted to take concomitant analgesics, except for limited doses of acetaminophen (as specified in Section 9.4.7)

Subjects will complete the diary-based Pain Rating Scale each morning (approximately 11 AM), 3 hours after taking their morning dose of study drug. They will return to the site for study procedures on Day 14 (Treatment Visit I), Day 21 (Treatment Visit II) and Day 35 (Treatment Visit III) and Day 49 (Treatment Visit IV). Procedures during Treatment Visits I, II, III, and IV will include collection of diaries (and issuance of the next set of diaries at Treatment Visits I, II and III) and efficacy and safety assessments: the site-based Pain Rating Scale, the Neuropathic Pain Scale, the Subject and Clinician Global Impression of Change (Treatment Visit IV only), the SF-36™ Health Status Survey (Acute) (Treatment Visit IV only), physical examination (Treatment Visit IV only), vital sign measurements and clinical laboratory tests (Treatment Visits I, III and IV), ABT-594 plasma assay collection (Treatment Visits I and IV only) and ECG (Treatment Visit IV only). A subset of subjects at selected sites will undergo intensive pharmacokinetic sampling at Treatment Visits I and IV.

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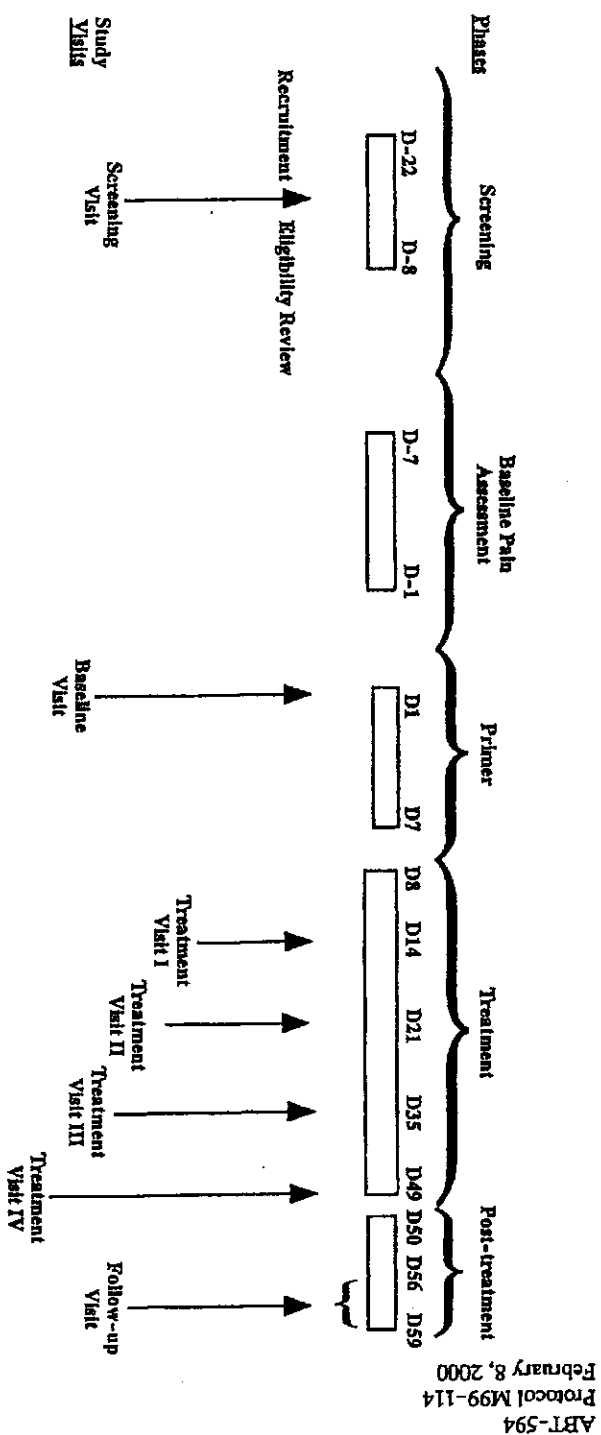
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On the day after Treatment Visit IV, subjects will enter the Post-Treatment Phase. Subjects will no longer take study drug or complete pain scales. Subjects may restart all discontinued medications under the guidance of their physician. Subjects will return for study procedures at the Follow-up Visit (7 to 10 days after their final study drug dose). Procedures at the Follow-up Visit will include physical examination, vital sign measurements, recording of any adverse events since Treatment Visit IV and re-examination of any abnormal ECG or clinical laboratory findings present at the previous evaluation.

For those subjects who participate in clinical studies of ABT-594 and who consent, a blood sample will be collected at Treatment Visit I in order to obtain a sample of genetic material (DNA). The DNA sample may be used at a later date to investigate associations between genetic differences (polymorphisms) and differences in the way subjects respond to treatment, in terms of efficacy or side-effects or both. If a genetic factor in response is identified, it may allow the development of a diagnostic test to identify those most likely to benefit before actually taking the drug. The sample may also be used to identify genes involved in painful diabetic polyneuropathy.

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**Figure 9.1a Study Schematic**

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## **9.2 Discussion of Study Design, Including the Choice of Control Groups**

The design of this study provides a placebo control group to assess the analgesic efficacy of ABT-594. Double-blind, parallel group designs are generally acknowledged as standard for unbiased estimates of treatment group differences. Validated pain scales will be employed.

## **9.3 Selection of Study Population**

It is anticipated that approximately 320 subjects will be randomized and receive study medication in this study. A subject may be randomized in this study provided that he/she meets all of the inclusion criteria outlined in Section 9.3.1 and does not meet any of the exclusion criteria in Section 9.3.2.

### **9.3.1 Inclusion Criteria**

9.3.1.1 Prior to any study specific procedure, voluntary written informed consent must be obtained from the subject after the purpose and nature of the study have been explained.

9.3.1.2 The subject must be age 18 or older and in relatively good health with a recent stable medical history.

9.3.1.3 The subject's weight must be  $\leq 265$  pounds.

9.3.1.4 A female subject must be non-lactating and:

- of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation),

OR

- of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and must continue contraceptive method through the course of the study).

All female subjects must have a negative  $\beta$  subunit human chorionic gonadotropin ( $\beta$ -hCG) at the Baseline Visit. Female subjects of childbearing potential must have a negative  $\beta$ -hCG at all Treatment Visits.

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- 9.3.1.5 The subject must have a diagnosis of diabetes mellitus (Type I or Type II) and a diagnosis of distal symmetric diabetic polyneuropathy.
- 9.3.1.6 The subject must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.
- 9.3.1.7 The location and quality of the pain under study are consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
- 9.3.1.8 The subject has distal symmetric diabetic polyneuropathy symptoms (including pain) which have been stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
- 9.3.1.9 The subject must have an average of  $\geq 4$  points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and  $\geq 4$  points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit.

### 9.3.2 Exclusion Criteria

- 9.3.2.1 The subject has positive test results for drugs of abuse or viral hepatitis at the Screening Visit, or has a known history of a positive test result for HIV.
- 9.3.2.2 The subject has recent ( $< 5$  years) history of drug or alcohol abuse or dependence.
- 9.3.2.3 The subject has an acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness.
- 9.3.2.4 The subject has active malignancy of any type or a history of malignancy (excluding basal cell carcinoma that has been treated or other malignancies that have been surgically removed and have had no evidence of recurrence for a minimum of 5 years prior to study start).
- 9.3.2.5 The subject has taken an investigational drug within 1 month prior to administration of study treatment or is scheduled to receive an investigational drug other than ABT-594 during the course of this study.

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- 9.3.2.6 The subject has a diastolic blood pressure greater than 95 mm Hg and/or a systolic blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.
- 9.3.2.7 The subject has orthostatic hypotension at the Screening Visit (as defined as a decrease in systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine to standing sustained after 1 minute of standing), or a history of syncope or pre-syncope symptoms.
- 9.3.2.8 The subject has previously participated in a study involving ABT-594, including the present study.
- 9.3.2.9 The subject has clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, including AST or ALT  $\geq 1.5$  times the upper limit of the reference range or a serum creatinine  $> 1.5$  mg/dL. Subjects may have elevated serum and urine glucose, but their serum glucose must have been under good control (in the opinion of the investigator) for at least the last 3 months prior to the Screening visit.
- 9.3.2.10 The subject has clinically significant electrocardiographic abnormalities.
- 9.3.2.11 The subject has ongoing treatment with or expected treatment with any medication not allowed as described in Section 9.4.7, including at least 7 days prior to the Baseline Pain Assessment Phase.
- 9.3.2.12 The subject has a diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular disease or other painful disorders affecting the extremities (other than the neuropathy under study) that the subject cannot differentiate from the neuropathy pain.
- 9.3.2.13 The subject has sympathetically maintained pain (e.g., Reflex Sympathetic Dystrophy, Causalgia), defined by the opinion of the investigator.
- 9.3.2.14 The subject is unlikely to comply with the study protocol or is unsuitable for any other reason, in the opinion of the investigator.

### 9.3.3 Removal of Subjects from Therapy

A subject may voluntarily terminate participation in the study at any time. The investigator may also decide, for medical reasons or protocol noncompliance, to

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terminate prematurely a subject's participation. The investigator must notify the CRA within 24 hours and document the reason for premature termination on the appropriate CRF.

Subjects, whose participation is terminated prematurely after signing study consent but before study drug administration, will not require follow-up observations. Subjects, whose participation is terminated prematurely after study drug administration must undergo procedures normally performed at Treatment Visit IV (see Table 9.5a) within 7-10 days following termination from the study.

If, in the judgment of Abbott Laboratories and possibly in consultation with the investigators, continued exposure to a study drug represents a significant risk to subjects, the study will be terminated.

## **9.4 Treatments**

### **9.4.1 Treatments Administered**

Subjects will be randomly assigned in an equal ratio to 1 of the following 4 treatment groups:

ABT-594 150 µg BID  
ABT-594 225 µg BID  
ABT-594 300 µg BID  
Placebo for ABT-594 BID

ABT-594 and matching placebo will be supplied as Light Gray Opaque No. 1 HGCs.

During the Primer Phase, subjects will receive a fixed dose escalation of ABT-594. ABT-594 will be initiated at 75 µg BID. The dose will increase every 2 days in 75 µg BID increments until subject are taking their assigned treatment dose (150, 225 or 300 µg BID). The ABT-594 dose escalation scheme is presented in Table 9.4.1a.

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**Table 9.4.1a ABT-594 Dose Escalation**

Treatment Regimen	Suggested Dosing Time	Days 1-7							Day 8
		1	2	3	4	5	6	7	
150 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
225 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
300 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg

Subjects will start study drug at PM dose on Day 1 (Section 9.4.5).

The number and type of HGCs per dose for the Treatment Phase is presented in Table 9.4.1b.

**Table 9.4.1b Number and Type of Capsules by Treatment Regimen**

Treatment Regimen		Number of Capsules Per Dose (Days 8-49)	
		Daily Blister Card (BID doses)	
		75 µg ABT-594 HGC	Placebo ABT-594 HGC
ABT-594	150 µg	2	2
ABT-594	225 µg	3	1
ABT-594	300 µg	4	0
Placebo		0	4

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#### 9.4.2 Identity of Investigational Products

**Table 9.4.2a Identity of Investigational Products**

Test Preparation Drug Product	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 75 µg HGC Formulation A-2	58-293-AR	52-015-KD-00	Abbott <sup>1</sup>
Placebo HGC No. 1, Light Gray Opaque (Starch)	55-243-AR-01	N/A	Abbott <sup>1</sup>

<sup>1</sup> Pilot Plant, North Chicago, Illinois

ABT-594 75 µg HGC and placebo HGC are identical in appearance, encapsulated in Light Gray Opaque capsule size No. 1 HGCs.

##### 9.4.2.1 Packaging and Labeling

Study drug supplies will be blinded and packaged in blister cards in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). Daily study medication cards will be provided to each subject.

Daily study medication cards will be labeled with the Module Number (assigned by Abbott, via IVRS), New Product Research Order (NPRO) number, Abbott address, study number, contents, storage conditions and directions for use.

Space will be provided on the label of each carton containing the daily study medication cards to record the subject initials and subject randomization number.

##### 9.4.2.2 Storage and Disposition of Supplies

All clinical supplies must be stored in a secure location until dispensed to a subject or until returned to Abbott Laboratories. All blinded study drug supplies must be stored at controlled room temperature (68-77°F, see USP).

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#### 9.4.2.3 Drug Accountability

The investigator or designee will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Clinical Supplies Invoice (CSI) or similar document. Study drug will be dispensed after randomization and assignment of study medication by IVRS (Section 9.4.3) for each subject who meets the enrollment criteria. The investigator or designee will record the subject number, subject initials and date dispensed to the subject on the Drug Accountability Form (Appendix E). The amount of study drug remaining will be recorded at Visits I, II, III and IV for each subject on the site Drug Accountability Form. An accurate running inventory of study drug will be kept and will include the NPRO number, CSI number(s), the number of modules dispensed and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the CRA throughout the study and at the site close-out visit. All used and unused supplies must be inventoried, accounted for and returned to Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with the instructions of the CRA, will also be included in the shipment. The investigator agrees not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator on FDA Form 1572.

#### 9.4.3 Method of Assigning Subjects to Treatment Groups

The randomization schedule will be computer-generated before the start of the study by Abbott Laboratories Department of Clinical Statistics. All subjects will be centrally randomized by investigative site using an Interactive Voice Response System (IVRS). Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each site.

Approximately 320 subjects will be randomized in an equal ratio to receive either ABT-594 150 µg BID, ABT-594 225 µg BID, ABT-594 300 µg BID or placebo. Subjects will be assigned randomization numbers in ascending numerical sequence per investigative site at the Baseline Visit.

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#### **9.4.4 Selection of Doses in the Study**

ABT-594 doses (150 µg, 225 µg, and 300 µg BID) were selected on the basis of Phase I and Phase II studies, and represent doses below the maximally tolerated dose. Phase II data suggested that ABT-594 doses greater than 75 µg BID may be efficacious in the relief of osteoarthritis and distal symmetrical neuropathy pain.

The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results. ABT-594 doses for the Primer Phase (75 µg, 150 µg, and 225 µg BID) were selected based on Phase I safety and pharmacokinetic data.

#### **9.4.5 Selection and Timing of Dose for Each Subject**

During the Primer Phase, subjects will start study drug at the evening dose on Day 1 within 1 hour following a meal (e.g., 8 PM). Subjects will then take BID doses of ABT-594 (75 µg, 150 µg, 225 µg or placebo during the Primer Phase and ABT-594 150 µg, 225 µg, 300 µg or placebo during the Treatment Phase) within 1 hour following a meal (e.g., at 8 AM and 8 PM).

Study drugs should be taken with at least one cup (8 ounces) of water.

#### **9.4.6 Blinding**

Both the investigator and the subject will remain blinded to the subject's treatment throughout the course of the study. The study blind may be broken if, in the opinion of the investigator, it is in the subject's best interest to know the study drug assignment. The sponsor (Abbott Laboratories) **MUST** be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. Blind breaking information will be provided using IVRS. Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each site. The sponsor must then be notified within 48 hours of the blind being broken. The date, and reason for blind breakage must be recorded on the appropriate CRF.

#### **9.4.7 Prior and Concomitant Therapy**

At the Screening Visit, a history of medications used over the prior 2 weeks will be taken.

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Concomitant analgesics (prescription or over-the-counter [OTC] except aspirin and acetaminophen as described below), including serotonin-specific reuptake inhibitors, tricyclic antidepressants, antiepileptic medications, sodium channel blockers (e.g., mexilitine), opioids, capsaicin, non-steroidal anti-inflammatory drugs, COX-2 inhibitors, muscle relaxants, TENS and topical analgesics will not be allowed.

Aspirin, 325 mg daily maximum, is permitted if taken for primary prevention of thromboembolic events and the dose has been stable for  $\geq 1$  month prior to the Baseline Visit. Acetaminophen, 3 grams daily maximum, or 6 grams maximum during the Baseline Pain Assessment Phase and per week, for each of the 7 weeks of the Primer and Treatment Phases, is permitted. Subjects will not be allowed to take analgesic medication (including acetaminophen) within 24 hours of the Baseline Visit and Treatment Visits I, II, III and IV.

If the administration of any concomitant medication is necessary during the course of this study, the medication name, dosage information, frequency and dates of administration must be reported on the CRF. Concomitant analgesic medication use (frequency only) will be recorded separately on the Concomitant Analgesic Medication Use CRF at the Baseline Visit and Treatment Visits I, II, III and IV. The concomitant medication use record will include the number of separate occasions each subject has used protocol-allowed (limited amounts) acetaminophen and any other analgesic (taken as a protocol violation) since the subject's previous visit.

#### **9.4.8 Treatment Compliance**

In order to document compliance with the treatment regimen, subjects will be instructed to return all medication cards and cartons (even if empty) to the study coordinator at Treatment Visits I, II, III and IV. Treatment compliance will be documented by the investigator or designee on the site Drug Accountability Form (Appendix E) and on the appropriate CRF.

Overdose information will be collected on the appropriate CRF.

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## **9.5 Efficacy, Pharmacokinetic and Safety Variables and Other Study Procedures**

### **9.5.1 Efficacy and Safety Measurements Assessed and Flow Charts**

Study procedures will be performed as summarized in Table 9.5a., Study Procedures Flow Chart.

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Table 9.5a Study Procedures Flow Chart

Study Activity	Screening Phase D-22 and D-8	Baseline Pain Assessment Phase D-7 to D-1	Primer Phase D1-D7	Treatment Phase D8-D49				Post-Treatment Phase D50-D59		
	Screening Visit		Baseline Visit D1	D2-D7	D8- D49	Treatment Visit			Follow-up Visit D56 to D59	
						D14 I	D21 II	D35 III		D49 IV
Informed Consent	X									
Medical History	X		X <sup>b</sup>							
Physical Exam	X <sup>c</sup>		X						X	
Vital Signs	X <sup>d</sup>		X <sup>e</sup>		X			X	X	
ECG			X					X	X <sup>f</sup>	
Clinical Laboratory Tests	X		X		X			X	X	X <sup>f</sup>
Viral Hepatitis Screen	X									
Urine Drug and Alcohol Screen	X									
Pregnancy Test			X							
Genetic Polymorphism Sample (If Applicable)			X		X <sup>h</sup>	X <sup>h</sup>		X <sup>h</sup>		
ABT-594 Plasma Assay					X			X		
ABT-594 PK Profile <sup>1</sup>					X			X		
Diary Issued	X		X		X	X				
Diary Collected			X		X	X				
Diary-Based Pain Rating Scale <sup>2</sup>		X		X						
Site-Based Pain Rating Scale			X		X	X		X	X	
Neuropathic Pain Scale			X		X	X		X	X	
Subject/Clinician Global Impression of Change									X	
SF-36™			X						X	
Randomize Patient			X							
Dispense Study Drug			X		X <sup>g</sup>	X		X		
Analgesic Use Monitoring			X		X	X		X	X	
Adverse Event Monitoring			X		X	X		X	X	X
Concomitant Medication Monitoring			X		X	X		X	X	X
Study Drug Accountability		X			X	X		X	X	X

<sup>a</sup> Or upon premature termination.  
<sup>b</sup> Inclusion history.  
<sup>c</sup> Includes height.  
<sup>d</sup> Includes orthostatic measurements at Screening Visit only.  
<sup>e</sup> Includes vital signs at Baseline Visit only.  
<sup>f</sup> Includes oral temperature at Baseline Visit only.  
<sup>g</sup> Performed only if there are clinically significant abnormalities at the previous evaluation.  
<sup>h</sup> Chemistry, hematology and urinalysis.

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#### **9.5.1.1 Efficacy Measurements**

Prior to any efficacy measurements, a trained site observer will instruct the subject on how to perform and record all pain assessments.

The baseline for all efficacy measurements (except for the diary-based Pain Rating Scale) will be the last evaluation performed prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to Day 1 of the study.

Efficacy assessments include the diary-based and site-based Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale and the Subject Global Impression of Change, Clinician Global Impression of Change, and SF-36™ Health Status Survey (Acute).

Efficacy measurements should be performed (when possible) 3-4 hours post dose.

#### **Pain Rating Scale (11-Point Likert Scale)**

Subjects will assess pain intensity daily by completing the Pain Rating Scale (Appendix F) in their diaries. These assessments will be completed daily at approximately the same time each morning (approximately 11 AM) during the Baseline Pain Assessment Phase and daily at the same time each morning (approximately 3 hours after the morning dose of study medication) during the Primer and Treatment phases. Subjects will record the time they completed these assessments in their diaries.

Subjects will also assess pain intensity by completing the Pain Rating Scale at the Investigative Site. These assessments will be completed at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature termination). The time of assessment will be recorded on the appropriate CRF.

#### **Neuropathic Pain Scale**

The Neuropathic Pain Scale (Appendix G) will be completed by subjects at the Baseline Visit and at Visits I, II, III, and IV (or upon premature termination).

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### **Subject Global Impression of Change**

The Subject Global Impression of Change (Appendix H) of analgesic relief due to study drug will be performed at Treatment Visit IV (or upon premature termination).

### **Clinician Global Impression of Change**

The Clinician Global Impression of Change (Appendix H) of a subject's analgesic relief due to study drug will be performed at Treatment Visit IV (or upon premature termination).

### **SF-36™ Health Status Survey (Acute)**

The SF-36™ Health Status Survey (Acute) will be completed by each subject at the Baseline Visit and at Treatment IV (or upon premature termination).

## **9.5.1.2 Safety Measurements and Procedures**

### **Informed Consent**

The investigator or designated representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject and by the person who administered the informed consent. A copy of the informed consent form will be given to the subject and a copy will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the subject received a signed copy.

### **Medical History**

A complete medical history will be obtained from each subject during the Screening Visit. In addition, history of tobacco and alcohol use, and medication (prescription or OTC) use over the 2 weeks prior to screening will be recorded. The medical history will be updated at the Baseline Visit.

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### **Physical Examination**

A physical examination, including weight, will be performed at the Screening Visit, Baseline Visit, Treatment Visit IV and at the Follow-up Visit. Height will be measured at the Baseline Visit only. The physical examination performed at the Baseline Visit will serve as the baseline physical examination.

### **Vital Signs**

Blood pressure, pulse rate and respiration rate will be measured at the Screening Visit, Baseline Visit, Visits I, III, and IV and at the Follow-up Visit. Orthostatic blood pressure and pulse rate will be measured at the Screening Visit only. Oral temperature will be taken at the Baseline Visit only. Vital sign measurements at the Baseline Visit will serve as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic) should be obtained after the subject has been sitting for at least 3 minutes. Orthostatic measurements should be obtained after 3 minutes in the supine position and then after 1 minute in the standing position. A cuff of suitable size should be applied evenly and firmly to the exposed upper arm. Subjects should not wear tight sleeves. Ideally, the subject's blood pressure should be measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurement should precede, not follow, scheduled blood draws. Subjects should be kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

### **Electrocardiogram (ECG)**

A resting 12-lead ECG will be obtained at the Baseline Visit and Treatment Visit IV. An ECG will be performed at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The ECG performed at the Baseline Visit will serve as the baseline ECG.

A qualified physician will interpret the ECG. One copy of each 12-lead ECG and physician's report will be retrieved by the CRA with the CRF.

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### Clinical Laboratory Testing

Samples will be obtained for the laboratory tests listed in Table 9.5.b at the Screening Visit, Baseline Visit (Day 1), and Treatment Visits I, III, and IV. Laboratory tests will be obtained at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The laboratory test results obtained at the Baseline Visit will serve as the baseline results. Blood draws should be performed after pain assessments or vital sign determinations during a visit.

**Table 9.5b Clinical Laboratory Tests**

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	BUN	Specific gravity
Hemoglobin	Creatinine	Ketones
Red Blood Cell (RBC) count	Total bilirubin	pH
White Blood Cell (WBC) count	Alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT)	Bilirubin
Neutrophils	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT)	Protein
Monocytes	Lactate Dehydrogenase (LDH)	Blood
Bands	Alkaline phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Hemoglobin A <sub>1c</sub> (Baseline Visit Only)	Chloride	
Lymphocytes	Calcium	
Mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH)	Inorganic phosphorus	
Platelet count (estimate not acceptable)	Uric Acid	
Prothrombin Time (PT)	Bicarbonate	
Partial Thromboplastin Time (PTT)	Cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests.

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The investigator will review all laboratory test results and will assess clinical significance for each abnormal result. All laboratory test results that are considered clinically significant by the investigator will be followed to a satisfactory resolution.

A copy of each laboratory report must be included with the CRF.

#### **Viral Hepatitis Screen**

Subjects will undergo serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody) at the Screening Visit. The hepatitis test panel will be performed by the central laboratory.

#### **Urine Drug Screen and Alcohol Screen**

Urine specimens will be tested for drugs of abuse and alcohol at the Screening Visit and will be performed by the central laboratory.

#### **Pregnancy Test**

A urine pregnancy test will be performed by designated study personnel at the Baseline Visit for all female subjects and at Visits I, II, III, and IV for female subjects of childbearing potential. A lactating or pregnant female will not be eligible for participation in this study.

#### **Adverse Events**

An adverse event is defined as any unexpected and unfavorable event such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of a drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject.

The subject will be instructed to contact the investigator if an adverse event occurs so that appropriate action can be taken and all adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject, will be reported on the appropriate CRF.

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The investigator will assess and record any adverse event in detail on the adverse event CRF including the date of onset, description, final diagnosis (if known), severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as sporadic, the events must be of similar nature and severity.

The investigator will use the following definitions to rate the severity of each adverse event:

**Table 9.5c Definitions for Investigator Rating of Adverse Event Severity**

Rating	Definition
Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

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**Table 9.5d Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug**

Rating	Definition
Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly, probably not, or not related to study drug is given, an alternate etiology must be provided for the adverse event.

Adverse events will be monitored continuously from the time of study drug administration to the Follow-up Visit. In addition, adverse events spontaneously reported to the investigator after completion of the Treatment Phase (or after premature termination) will be collected up to 30 days after drug discontinuation and reported to Abbott Laboratories. Subjects will be instructed to report to the investigator any other adverse events that occur after Follow-up Visit.

Serious adverse events, as well as adverse events that the investigator considered to be related to study design and/or procedures that occur after signing the Informed Consent and prior to the first dose of study drug will also be collected.

Any abnormal laboratory value or change in vital signs will not be documented as an adverse event unless it is a reason for premature discontinuation from the study, requires treatment, or meets regulatory criteria for a serious adverse event.

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Ongoing medical conditions will be considered adverse events if there is an increase in severity or frequency of occurrence. Since measurements of pain intensity are efficacy measurements in this study, an increase in severity or frequency of occurrence of the pain under study will not be considered adverse events for the purposes of this study.

#### **Serious Adverse Events**

If an adverse event meets any of the following criteria, it is to be reported to Abbott Laboratories as a serious adverse event (SAE) within 24 hours of occurrence or notification to the site:

Death of Subject:	An event which results in the death of a subject.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility.
Prolongation of Hospitalization:	An event which occurs while the study subject is hospitalized and that prolongs the subject's hospital stay.
Persistent or Significant Disability/Incapacity:	An event which results in a condition that interferes with the activities of daily living of a study subject (e.g., permanent loss of vision).

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**Thomas Exhibit 5**

**D's Exhibit 534**

**Part 2**

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Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, miscarriage/spontaneous and elective abortions will be reported to Abbott Laboratories as serious adverse events.

In the event of a serious adverse event, whether related to study drug or not, the investigator and other professional personnel in attendance will be notified as soon as possible for the appropriate action. The investigators will notify by telephone, one of the following people at Abbott Laboratories within 24 hours of being made aware of any serious adverse event.

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Bruce G. McCarthy, M.D.  
Associate Medical Director  
Analgesia Venture  
Dept. 48Q, Bldg. AP34  
200 Abbott Park Road  
Abbott Park, Illinois 60064-6193  
Office: (847) 935-6244  
Home: (773) 529-5729  
Fax: (847) 938-5258

Christopher J. Silber, M.D.  
Venture Head  
Analgesia Venture  
Dept. 48Q, Bldg. AP34  
200 Abbott Park Road  
Abbott Park, Illinois 60064-6193  
Office: (847) 938-5236  
Home: (847) 615-0428  
Fax: (847) 938-5258

Fred Siebert  
Sr. Clinical Research Associate  
Analgesia Venture  
Dept. 48Q, Bldg. AP34  
200 Abbott Park Road  
Abbott Park, Illinois 60064-6193  
Office: (847) 938-1167  
Home: (847) 298-4682  
Fax: (847) 938-5258

In addition, a written confirmation of the occurrence, including any supplementary data, must be sent within 3 days of the telephone report to:

Bruce G. McCarthy, M.D.  
Dept. 48Q, Bldg. AP34  
Abbott Laboratories  
200 Abbott Park Road  
Abbott Park, IL 60064-6193  
Fax: (847) 938-5258

#### **9.5.2 Appropriateness of Measurements**

All efficacy measurements in this study are validated and are considered standard for this population. All clinical and laboratory procedures in this study are standard and generally accepted.

#### **9.5.3 Efficacy Variables**

All efficacy variables will be derived from the efficacy measurements (Section 9.5.1.1).

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#### **9.5.3.1 Primary Variable(s)**

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. The baseline pain score for the diary data is defined as the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1 of the study.

#### **9.5.3.2 Secondary Variable(s)**

Change from baseline to final and each scheduled evaluation will be calculated for each of the following secondary efficacy variables:

- Diary-based Pain Rating Scale (11-Point Likert), change from baseline to each evaluation only
- Site Based Pain Rating Scale (11-Point Likert)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health]<sup>4</sup> PCS, and MCS.<sup>5</sup>

The pain evaluations recorded at the Baseline Visit will be used as the baseline score for pain evaluations assessed at the investigative site.

#### **9.5.4 Drug Concentration Measurements**

##### **9.5.4.1 Collection, Processing and Storage of Blood Samples for ABT-594 Plasma Assay**

Blood samples for ABT-594 plasma assay will be collected from all subjects at Treatment Visits I and IV. One blood sample (approximately 7 mL) will be collected into a sodium heparin evacuated collection tube at each visit. Blood draws should be

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performed after any pain assessments or vital sign determinations during a visit. For subjects who prematurely discontinue, a blood sample will be taken for ABT-594 assay at the premature discontinuation visit, and the exact times at which the dose was taken will be recorded.

All blood samples will be immediately stored at 4°C or below. The samples will be separated by centrifugation within one hour after sample collection. The supernatant will be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, subject number, initials, and date and time of sample collection. This information will also be recorded on the appropriate CRF. All labeled plastic vials will be placed in a rack to prevent breakage. **Plasma samples for determination of ABT-594 must be frozen at -5°C or colder within one hour from centrifugation.** All specimens will be kept frozen at -5°C or colder until packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories.

The time and date of each subject's morning dose on the day of plasma assay blood draw, the time and date of the meal eaten prior to the morning dose, and the time and date of the evening dose on the day prior to the plasma assay blood draw will be recorded in the CRF.

#### 9.5.4.2 Additional Pharmacokinetic Sampling

For those subjects participating in the additional pharmacokinetic sampling for PK profile (approximately 30 subjects), blood samples will be collected at Treatment Visits I and IV.

After establishing the time of the Treatment Visit, the subject will be instructed to take the preceding day's study drug as close as possible to 8 PM. At the office visit, the study medication will be taken in the presence of the office staff in order to allow proper and accurate recording of blood collection times relative to dosing. The time of the visit should accommodate a target time for the morning dose of 12 hours after the preceding evening's dose. Blood samples will be collected as follows: just prior to dosing (0 hour)

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and at 1.5, 3, 5, and 8 hours after the morning dosing. Subjects will receive their 8 PM dose as scheduled. Subjects will be confined at the site until the blood sample at the 8 hour time point is collected. Pharmacokinetic profile samples will be processed and stored as specified in Section 9.5.4.1 until shipment to Abbott Laboratories.

#### **9.5.4.3 Shipment of Plasma Samples**

An inventory list of the samples included in the shipment must accompany the shipment. The inventory list will include the shipping date, number of samples in the container, drug identification, Abbott protocol number, subject numbers, sample type, sampling times, and missing samples. The frozen samples will be packed in dry ice sufficient to last 2 days during shipping.

Arrangements will be made with Abbott Laboratories for shipping of the plasma samples to the following Abbott address:

Sample Receiving  
Abbott Laboratories  
Dept. 4TA, Bldg. AP9  
100 Abbott Park Road  
Abbott Park, IL 60064-6122  
Phone: (847) 937-0889  
Fax: (847) 938-9898

On the day of shipping, a copy of the inventory sheet should be faxed to the Sample Receiving Department at (847) 938-9898.

#### **9.5.5 Blood Samples for Genetic Polymorphism Analysis**

Two 10 mL whole blood samples will be collected in purple top (EDTA) tubes at the Baseline Visit and shipped immediately at ambient or refrigerated temperature to:

Covance Central Laboratory Services  
8211 SciCor Drive  
Indianapolis, IN 46214

If clear differences in response are noted during the clinical development of ABT-594 and believed to be genetically related, these samples may be analyzed as part of a multicenter, multistudy project to identify genetic factors involved in the response to

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ABT-594 or drugs of this class. The specific response may be related to efficacy or safety, or both. The results of this potential analysis will not be reported with the study summary. The samples may also be used for development of a diagnostic test for drug response.

The pharmacogenetic analyses involve two methods: one which examines known genes believed to be involved in the particular response (Candidate Gene), and one which uses a high density marker map to locate and identify genes related to the response (Genomic Association) by comparing the marker profile between the subjects with an effect and a corresponding negative control group. The Candidate Gene method includes genes related to drug metabolism, drug targets or target pathways, and others including genes relating to cellular homeostasis. The Genomic Association method utilizes a map of single nucleotide polymorphisms which by themselves are essentially meaningless, but when correlated with groups of two distinct subject groups allow the identification of the gene(s) related to the difference between the groups. For the purpose of pharmacogenetic studies such as this, the difference would be related to the response to the drug or the presence or absence of the disease being tested.

## 9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting will be held with Abbott personnel, the investigators and their study coordinators, the CRO's project manager and CRAs. This meeting will entail a detailed discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel at each site will be trained on the study procedures by a CRA at a study initiation visit and be given a CRF completion workbook for reference. The CRAs will monitor each site approximately every 4 weeks. At each visit, 100% source-document review will be made against the entries on the CRFs and a quality-assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. The investigator must agree to provide Abbott Laboratories (or designee) access to all source documents in order to verify CRF entries. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

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The SF-36™ Health Status Survey (Acute) will be recorded directly on the CRF and will be considered source data.

All CRFs must be legible and completed in black ball point ink. All corrections must be initialed and dated by the investigator or designated assistant. The investigator will review the CRFs for completeness and accuracy and sign and date the set of case report forms where indicated.

Each CRF will be printed on 3-part NCR paper. The forms consist of a white, yellow and pink copy. The white and yellow copy of the completed, verified CRF will be collected by the CRA and the pink copy retained at the investigative site.

Data captured on the CRF will be entered into the database by a double-key entry procedure at Abbott Laboratories. Discrepancies against the hard-copy CRF will be reviewed and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values, and any necessary corrections will be made to the database and documented via addenda or audit trail.

The laboratory results will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

## **9.7 Statistical Methods and Determination of Sample Size**

### **9.7.1 Statistical and Analytical Plans**

All statistical tests will be 2-tailed and considered statistically significant if the P-value (Type 1 error rate) is less than or equal to 0.05 (when rounded to 3 decimal places).

For all efficacy and safety endpoints, comparisons of primary interest will be between each ABT-594 dose group and the placebo group, along with an assessment of ABT-594 linear dose response. Appropriate secondary comparisons will be made as considered necessary. No statistical adjustments will be made for multiple comparisons.

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The baseline for all variables (except for the diary-based Pain Rating Scale) will be the last measurement obtained prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1.

#### **9.7.1.1 Data Sets Analyzed**

Efficacy analyses will be performed for 2 sets of data: intent-to-treat subjects and evaluable subjects. Subjects receiving at least 1 dose of study drug with at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert) will be included in the intent-to-treat analyses. The evaluable dataset will include subjects that receive at least 7 days of study drug with at least 1 baseline and at least 1 post Day 7 pain assessment for the diary-based Pain Rating Scale. Safety analyses will be performed with all randomized subjects who receive at least 1 dose of study drug.

#### **9.7.1.2 Demographic and Other Baseline Characteristics**

Baseline comparability among treatment groups for the reasons for premature discontinuation, demographic and baseline pain assessment measurements will be assessed. The analyses will be performed using 1 or more of the following methods: a 1-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables, the Cochran-Mantel-Haenszel (CMH) test for equal row means for ordered categorical variables, and the Fisher's exact test (or its generalization to  $r \times c$  tables) for qualitative variables.

#### **9.7.1.3 Efficacy Analyses**

For all efficacy variables (except the diary-based Pain Rating Scale), the baseline measurement will be the last measurement obtained prior to receiving the first dose of blinded study drug on Day 1. Baseline for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to Day 1 of the study. Change from baseline to each scheduled evaluation will be calculated for all efficacy variables (except both Global Impression of Change scores).

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### **Primary Efficacy Analysis**

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert) score from each subject's diary to the corresponding average of the last 7 days on study drug.

Treatment groups differences for the primary efficacy variable will be evaluated using a 2-way ANOVA with factors for treatment group, study center, and the treatment group by study center interaction. If the interaction term is not statistically significant at the 0.10 level, the primary efficacy analysis for the treatment group differences will be the 2-way ANOVA with factors for treatment group and study center, but without the interaction term. If some study centers have fewer than 1 subject per treatment group in the intent-to-treat dataset, data from such centers will be combined for analysis.

### **Secondary Efficacy Analysis**

Treatment group differences in the mean change from baseline to the final evaluation for the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), including 8 sub-domains and PCS and MCS, and the site-based Pain Rating Scale (11-Point Likert) score will be assessed using a 2-way ANOVA as described in the above Primary Efficacy Analysis subsection. The actual scores of each of the Subject and Clinician Global Impression of Change will be analyzed using the CMH test for equal row means with study centers as strata. SF-36™ PCS and MCS may also be analyzed using appropriate regression analysis (with possible factors for demographic variables, treatment and time).

Additionally, treatment group differences in the change from baseline to each scheduled evaluation will be assessed, as described for the change from baseline to the final evaluation for the Neuropathic Pain Scale and the site-based Pain Rating Scale (11-Point Likert). For the diary-based Pain Rating Scale (11-Point Likert), change from baseline to each scheduled evaluation will be analyzed using the last 7 days prior to each scheduled visit. Subject and Clinician Global Impression of Change will be evaluated using CMH methodology on actual scores.

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If indicated, exploratory analyses will be performed on change from baseline pain scores, such as analysis of covariance (ANCOVA), with baseline pain scores as the covariate.

Dose response for ABT-594 will be explored using both a parametric regression model and nonparametric tests, with and without placebo included. If the effect of investigator sites is not significant, then the nonparametric Jonckheere-Terpstra test will be used instead of Page's test to assess dose response of ABT-594.

Other analyses will be performed as appropriate.

### Missing Data

Two sets of analyses, corresponding to the handling of missing observations, will be performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses will use the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis will have data for each specified evaluation. This technique reduces the bias caused by subjects who prematurely terminate for lack of efficacy. The "observed cases" (OC) analysis will not estimate the missing evaluation, and a subject who does not have pain evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

In the event of data missing from the individual items in the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute), the estimated score of the missing item will be calculated, when less than one-half (within the scale of interest) of items are non-missing, as follows:

1. Calculate the ratio of the total score of the scale (the non-missing items) divided by the maximum possible total score for the non-missing items,
2. Multiply the maximum possible scores for the missing item by the ratio obtained in Step 1 above.

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#### 9.7.1.4 Safety Analyses

All subjects receiving at least 1 dose of study drug will be evaluated for safety.

Adverse events will be coded using the COSTART V<sup>6</sup> dictionary. Treatment-emergent adverse events (i.e., those which begin or worsen in severity after randomized study drug is taken) will be tabulated by body system and COSTART term for each treatment group. Treatment group differences will be evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. A summary of the severity, relationship to study drug, incidence and prevalence across time of all treatment-emergent adverse events, tabulated by COSTART term and body system, will be presented for each treatment group. Analyses by subgroup will be performed as appropriate.

Laboratory data will be analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses will be on the change from baseline to the minimum, maximum and final values during the study for each laboratory variable.

Additionally, the number and percentage of subjects with shifts from baseline to the final values using criteria for limits for statistical analysis and normal ranges to define categories (low, normal, high and missing) will be summarized.

Laboratory data values will be categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values will be flagged in the data listings. In addition, laboratory results which satisfy the criteria for limits for statistical analysis (Appendix I) will be identified.

Mean changes from baseline to the minimum, maximum and final values for vital signs and ECG will be analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfy the criteria for below and above limits (Appendix I) will be identified.

Concurrent medication use will be summarized by treatment group.

Additional safety analyses will be performed as indicated.

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### 9.7.2 Determination of Sample Size

The study is designed to enroll approximately 320 subjects (approximately 80 subjects in each treatment group). This sample size will allow for the detection of a 0.46 effect size in the average diary-based Pain Rating Scale score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation is based on results obtained from Study M98-833 of ABT-594 and published data using Gabapentin for subjects with painful diabetic polyneuropathy<sup>7</sup> and assuming a 39% and 25% improvement from baseline for ABT-594 and placebo, respectively.

### 9.7.3 Pharmacokinetics/Pharmacodynamics

The maximum observed plasma concentration ( $C_{max}$ ), the time to  $C_{max}$  ( $T_{max}$ ), and the trough plasma concentration ( $C_{trough}$ ) will be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve during a dosing interval (AUC) will be obtained by the trapezoidal rule, using the Hour 0 concentration value for the Hour 12 value, or by some other appropriate methodology.

To assess dose proportionality and time invariance,  $T_{max}$ , dose-normalized  $C_{trough}$  and log-transformed dose-normalized AUC and  $C_{max}$  from the subset of subjects participating in the additional pharmacokinetic (PK) sampling will be subjected to a mixed effects model analysis. The model will include dose, visit (Visit I and Visit IV), and dose by visit interaction as fixed effects. Age, body weight, nicotine use status, and other variables that might account for variability in pharmacokinetics will be included as covariates. The study center factor will be included in the initial model, including a center main effect and, as appropriate, interaction of center with other factors. The center factor, or at least the interaction terms involving center, may be dropped from the model if they explain little of the variability in the data. If the number of subjects who have only Visit I data and not Visit IV data exceeds 20% of the subjects with intensive PK sampling, then analyses will also be performed for each visit separately. The hypothesis of invariance with dose will be tested by comparing the 300 µg BID dose vs the 150 µg BID dose. If the hypothesis of dose proportionality is rejected in a comparison, then the

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225 µg BID dose will be compared to each of the 150 and 300 µg BID doses. If the visit by dose interaction is statistically significant, then a comparison will be made for each visit.

An exploratory analysis will also be performed on the data set obtained from all subjects (including those who do not participate in the intensive PK sampling). This analysis will appropriately take into account the time of sampling relative to dosing. The questions of dose proportionality and change from Visit I to Visit IV will be considered in this analysis.

If there is some evidence from the data of this study that ABT-594 is efficacious, then the relationship between ABT-594 plasma concentration and the primary efficacy variable will be explored, using data from ABT-594 and placebo treatment groups or from ABT-594 treatment groups alone. One exploration will utilize the data of all subjects. An analysis using only the data of subjects undergoing intensive PK sampling may also be done. The model will include effects for efficacy variable baseline value and for visit. The center factor will be incorporated appropriately. The dependency of the measurements from the same subject will be accounted for.

Other analyses may be performed as necessary.

## **9.8 Changes in the Conduct of the Study or Planned Analyses**

### **9.8.1 Protocol Changes**

This study will be conducted in accordance with the protocol, GCP, all applicable local, state federal regulations and regulatory requirements. Neither the investigator nor the CRO will modify this protocol without first obtaining the concurrence of Abbott Laboratories. The modification must be documented in writing. Any change in the research activity, except those necessary to remove an apparent immediate hazard to the subject or those of an administrative or clarifying nature, must be reviewed and approved by the Institutional Review Board before implementation. Abbott Laboratories must submit protocol amendments to the FDA and possibly to other government agencies.

This study will be terminated if these conditions are not met.

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## **10.0 Protocol Deviations**

When deviation from the protocol is deemed necessary for an individual subject, the investigator or other physician in attendance must contact the site study monitor at the CRO, who will contact Abbott Laboratories. Such contact will be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study. Any departures from the protocol will be authorized only for that one subject. A description of the departure from the protocol and the reason for it will be recorded on the CRF.

## **11.0 Use of Information and Publication**

All information concerning ABT-594 and Abbott Laboratories' operations, such as Abbott Laboratories' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of ABT-594. This information may be disclosed as deemed necessary by Abbott Laboratories. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Abbott Laboratories with complete test results and all data developed in this study.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

Should the investigator choose to publish the results of this study, a copy of the manuscript will be provided to Abbott Laboratories at least 90 days before the date of submission to the intended publisher.

Neither the subject nor their physician will be informed of individual subject pharmacogenetic results, should they be performed, nor will anyone not directly involved in this research. This is due to the fact that, 1) the subject and their physician are already

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aware of the subject's particular response to the drug and the study information would not affect their future medical care, and 2) if an association is established between a genetic sequence and a treatment response, separate studies must be conducted in order to validate or confirm the results and the properties of the test prior to the necessary regulatory approval to use the test for diagnostic purposes. DNA samples from this protocol may be used either for gene identification, validation, or diagnostic test development studies, as well as discovery of genes related to painful diabetic polyneuropathy.

## 12.0 Completion of The Study

The investigator will complete and report this study in satisfactory compliance with the protocol within 9 months after receipt of study supplies. Continuation of the study beyond this time must be mutually agreed upon in writing by both the investigator and Abbott Laboratories. It is agreed that, for reasonable cause, either the investigator or Abbott Laboratories (the sponsor), may terminate this study prematurely provided that written notice is submitted at a reasonable time in advance of the intended termination.

The investigator will retain all essential documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are not pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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### 13.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for ABT-594.
2. I have read the protocol and agree to conduct the study as outlined and in accordance with all local, state, and federal regulations.
3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

\_\_\_\_\_  
Signature of Principal Investigator

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Principal Investigator (printed or typed)

IN/R-S/1/ABT594/99114/99114PRO/P25-49  
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## Appendix A

### Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott Laboratories has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed protocol for the study.
2. A signed Form FDA 1572 or equivalent document certifying the investigator's agreement to comply with U.S. Federal (21 CFR, ICH GCP Guidelines) regulations governing the conduct of the study.
3. A signed Abbott Financial Disclosure form.
4. A current curriculum vitae of the investigator. If sub-investigators will participate in the study, a curriculum vitae for each.
5. Requirements for the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
  - A copy of the letter of approval of the IRB/IEC. The letter must specify that both the protocol and consent form were approved.
  - The names and affiliations of the members of the IRB/IEC or assurance number.
  - If the principal and/or sub-investigator is a member of the IRB/IEC, a letter stating that he/she did not participate in the review or approval of the protocol or consent form.
6. A specimen copy of the IRB/IEC-approved informed consent document to be used in the study.
7. A list of normal ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.
8. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

As a rule, these documents will be provided in the course of one or more visits to the investigator by an Abbott Laboratories representative. Usually the study cannot begin until all of the documents listed above have been provided.

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## **Appendix B**

### **Declaration of Helsinki**

#### **Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects**

Adopted by the 18th World Medical Assembly, Helsinki, Finland, in June 1964.  
Amended by the 29th World Medical Assembly, Tokyo, Japan, in October 1975,  
35th World Medical Assembly, Venice, Italy, in October 1983,  
41st World Medical Assembly, Hong Kong, in September 1989 and  
48th General Assembly, Somerset West, Republic of South Africa 1996.

#### **Introduction**

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

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## **Appendix B (Cont.)**

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

### **I. Basic Principles**

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

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### **Appendix B (Cont.)**

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obligated to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in the Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.
10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

#### **II. Medical Research Combined with Professional Care (Clinical Research)**

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

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2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician - patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I.2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

### **III. Non-Therapeutic Biomedical Research Involving Human Patients (Non-Clinical Biomedical Research)**

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

REASON FOR REVISION: Revised to correspond to the amendment adopted by the 48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa 1996.

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## **Appendix C**

### **Responsibilities of the Clinical Investigator**

Clinical research studies sponsored by Abbott Laboratories are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is actually a form letter addressed to the sponsor (Abbott Laboratories), summarizing the investigators qualifications for the study and their willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the investigator agrees to assume the following responsibilities:

1. To secure prior approval of the study by an appropriate institutional review board which conforms to FDA regulations.
2. To make at least yearly reports on the progress of the study to the above committee, and a final report within three months of study completion.
3. To maintain current running records of the receipt, administration, and disposition of study medication and to return all unused study medication to Abbott Laboratories.
4. To obtain valid written informed consent from each patient who participates in the study.
5. To prepare and maintain adequate case histories of all persons entered into the study, including case report forms, hospital records, laboratory results, etc., and to maintain these data for a minimum of two years following notification by Abbott Laboratories that all investigations have been discontinued with this drug.
6. To identify all subinvestigators who will also supervise drug administration.
7. To report adverse effects to Abbott Laboratories promptly. In the event of serious or unexpected adverse event, to notify Abbott Laboratories immediately by telephone.
8. To allow possible inspection and copying by the FDA of case reports and records of drug distribution.

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## **Appendix D**

### **Elements of the Consent Form**

Abbott Laboratories requires that all informed consent statements used in studies which they sponsor comply with FDA 21 CFR 50 (Protection of Human Subjects) and the ICH Good Clinical Practice Guideline. To ensure compliance, the informed consent itemization listed below is provided to guide the investigator in drafting an acceptable informed consent. Abbott Laboratories will review a proposed informed consent prior to its submission to the Review Committee (Institutional Review Board, Ethics Committee); alternatively, Abbott will supply to the investigator a draft informed consent statement which may be submitted to the review Committee.

For IND Studies, procedures will comply with FDA 21 CFR 50 and the ICH Good Clinical Practice Guideline.

Signed informed consent will be obtained from all patients participating in PPD Clinical Research studies or the patients' legally authorized representative. This consent must include the following items:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The approximate number of patients involved in the trial.
4. The expected duration of the patient's participation.
5. The trial treatment(s) and the probability for random assignment to each treatment.
6. Identification of experimental procedures.
7. The trial procedures to be followed, including all invasive procedures.
8. The patient's responsibilities.
9. A description of any reasonably foreseeable risks or inconveniences to the patient and, if applicable, to an embryo, fetus, or nursing infant.
10. A statement that may involve risks which are currently unforeseeable.
11. The anticipated expenses, if any, to the patient for participating in the trial.
12. A description of the reasonable expected benefits. If there is no intended clinical benefit to the patient, this should be stated.

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### Appendix D (Cont.)

13. The anticipated prorated payment, if any, to the patient for participating in the trial.
14. The alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks.
15. A statement that the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the trial.
16. An explanation as to whether any compensation or medical treatment are available if injury occurs. If so, what the compensation consists of and/or where further information may be obtained.
17. Whom to contact about information regarding the trial.
18. Whom to contact about research patient's rights (ideally not the investigator).
19. Whom to contact in the event of trial-related injury of the patient.
20. A statement that the monitor(s), auditor(s), the IRB/EC, and regulatory authorities (e.g., FDA) will be granted direct access to the patients' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the patient or the patient's legally acceptable representative is authorizing such access.
21. A statement that the site will collect information on the patient per ICH requirements, including patient name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency will also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site.
22. A statement that the records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.
23. The foreseeable circumstances and/or reasons under which the patients' participation in the trial may be terminated.

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24. Procedures for orderly termination of participation.
25. A statement that participation is voluntary.
26. A statement that refusal to participate will involve no penalty or loss of benefits.
27. A statement that the patient may discontinue participation at any time without penalty or loss of benefits.
28. A statement that a signed and dated copy of the consent is given to the patient.
29. The statement, "I agree to participate..."
30. A place for the patient or the patient's legally acceptable representative to sign and date.
31. A place for the person who conducted the informed consent discussion to sign and date.

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Subject Randomization Number: ◆ \_\_\_\_\_

Subject Initials: \_\_\_\_\_

Subject Birthdate: \_\_\_\_\_

**Investigator's Name:** \_\_\_\_\_

**Location:** \_\_\_\_\_

	Module Carton Type	Module # ♦	NPRO #	Clinical Supplier Invoice No.	Date Received (M/D/Y)
Baseline Visit	Days 1-7				
Baseline Visit	Days 8-49				
Visit II	Days 8-49				
Visit III	Days 8-49				

DISPENSED TO SUBJECT					RETURNED FROM SUBJECT			VERIFIED BY CRA		
Visit	Module # ♦	# Capsules	Date	By*	Checked By	Date	No. of Capsules Remaining	By*	By†	Date
Baseline Visit	Days 1-7	52								
	Days 8-49	144								
	Redispense balance of Days 8-49 cards remaining from Baseline Visit									
Visit I										
Visit II		144								
Visit III		144								

• Pharmacist/Coordinator/Nurse

+ CRO Monitor

♦ Assigned by IVRS

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## **Appendix F**

### **Pain Assessments**

#### **Pain Rating Scale (11 point Likert)**

The subject's pain intensity will be assessed by completion of the following statement in the daily diaries and at the investigative site.

How severe was your neuropathy pain during the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Possible

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## Appendix G

### Neuropathic Pain Scale

**Instructions:** There are several different aspects of pain which we are interested in measuring: pain sharpness, heat/cold, dullness, intensity, overall unpleasantness, and surface vs. deep pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree on how *sweet* a piece of pie might be (the *intensity* of the sweetness), but some might enjoy it more if it were sweeter while others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quiet and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. In short, the *intensity* of a sensation is not the same as how it makes you feel. A sound might be unpleasant and still be quiet (think of someone grating their fingernails along a chalkboard). A sound can be quiet and "dull" or loud and "dull."

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, *how much* it hurts and *how unpleasant* or annoying it is. Although often the intensity of pain has a strong influence on how unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very bad about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at all dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate very high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactly what you experience.

1. Please use the scale below to tell us how intense your pain is. Place an "X" through the number that best describes the intensity of your pain.		The most intense pain sensation imaginable											
No pain	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; text-align: center;">0</td> <td style="width: 20px; text-align: center;">1</td> <td style="width: 20px; text-align: center;">2</td> <td style="width: 20px; text-align: center;">3</td> <td style="width: 20px; text-align: center;">4</td> <td style="width: 20px; text-align: center;">5</td> <td style="width: 20px; text-align: center;">6</td> <td style="width: 20px; text-align: center;">7</td> <td style="width: 20px; text-align: center;">8</td> <td style="width: 20px; text-align: center;">9</td> <td style="width: 20px; text-align: center;">10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10	
0	1	2	3	4	5	6	7	8	9	10			
2. Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts."		The most sharp sensation imaginable ("like a knife")											
Not sharp	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; text-align: center;">0</td> <td style="width: 20px; text-align: center;">1</td> <td style="width: 20px; text-align: center;">2</td> <td style="width: 20px; text-align: center;">3</td> <td style="width: 20px; text-align: center;">4</td> <td style="width: 20px; text-align: center;">5</td> <td style="width: 20px; text-align: center;">6</td> <td style="width: 20px; text-align: center;">7</td> <td style="width: 20px; text-align: center;">8</td> <td style="width: 20px; text-align: center;">9</td> <td style="width: 20px; text-align: center;">10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10	
0	1	2	3	4	5	6	7	8	9	10			
3. Please use the scale below to tell us how hot your pain feels. Words used to describe very hot pain include "burning" and "on fire."		The most hot sensation imaginable ("on fire")											
Not hot	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; text-align: center;">0</td> <td style="width: 20px; text-align: center;">1</td> <td style="width: 20px; text-align: center;">2</td> <td style="width: 20px; text-align: center;">3</td> <td style="width: 20px; text-align: center;">4</td> <td style="width: 20px; text-align: center;">5</td> <td style="width: 20px; text-align: center;">6</td> <td style="width: 20px; text-align: center;">7</td> <td style="width: 20px; text-align: center;">8</td> <td style="width: 20px; text-align: center;">9</td> <td style="width: 20px; text-align: center;">10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10	
0	1	2	3	4	5	6	7	8	9	10			
4. Please use the scale below to tell us how dull your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching" and "like a bruise."		The most dull sensation imaginable											
Not dull	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; text-align: center;">0</td> <td style="width: 20px; text-align: center;">1</td> <td style="width: 20px; text-align: center;">2</td> <td style="width: 20px; text-align: center;">3</td> <td style="width: 20px; text-align: center;">4</td> <td style="width: 20px; text-align: center;">5</td> <td style="width: 20px; text-align: center;">6</td> <td style="width: 20px; text-align: center;">7</td> <td style="width: 20px; text-align: center;">8</td> <td style="width: 20px; text-align: center;">9</td> <td style="width: 20px; text-align: center;">10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10	
0	1	2	3	4	5	6	7	8	9	10			

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### Appendix G (Cont.)

5.	Please use the scale below to tell us how cold your pain feels. Words used to describe very cold pain include "like ice," and "freezing."											
Not cold	0	1	2	3	4	5	6	7	8	9	10	The most cold sensation imaginable ("freezing")
6.	Please use the scale below to tell us how sensitive your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."											
Not sensitive	0	1	2	3	4	5	6	7	8	9	10	The most sensitive sensation imaginable ("raw skin")
7.	Please use the scale below to tell us how itchy your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."											
Not itchy	0	1	2	3	4	5	6	7	8	9	10	The most itchy sensation imaginable ("like poison oak")
8.	Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how unpleasant your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable." Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how unpleasant your pain feels.											
Not unpleasant	0	1	2	3	4	5	6	7	8	9	10	The most unpleasant sensation imaginable ("intolerable")
9.	Lastly, we want you to give us an estimate of the severity of your <u>deep</u> versus <u>surface</u> pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.											
<b>HOW INTENSE IS YOUR DEEP PAIN?</b>												
No deep pain	0	1	2	3	4	5	6	7	8	9	10	The most intense deep pain sensation imaginable
<b>HOW INTENSE IS YOUR SURFACE PAIN?</b>												
No surface pain	0	1	2	3	4	5	6	7	8	9	10	The most intense surface pain sensation imaginable

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## **Appendix H**

### **Subject Global Impression of Change and Clinician Global Impression of Change**

#### **Subject Global Impression of Change**

The subject's impression of pain relief will be assessed by completion of the following statement:

Compared to the Baseline Pain Assessment Phase, how much have you changed overall?

- 1 Much Improved
- 2 Moderately Improved
- 3 Minimally Improved
- 4 No Change
- 5 Minimally Worse
- 6 Moderately Worse
- 7 Much Worse

#### **Clinician Global Impression of Change**

The clinicians impression of pain relief will be assessed by completion of the following statement:

Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to Baseline, how much has the subject changed overall?

- 1 Much Improved
- 2 Moderately Improved
- 3 Minimally Improved
- 4 No Change
- 5 Minimally Worse
- 6 Moderately Worse
- 7 Much Worse

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**Appendix I**  
**Laboratory Determinations, Vital Signs and Electrocardiogram**  
**Variables for Statistical Analysis**

Hematology	Below Limit	Above Limit
Hemoglobin (g/dL)		
Female	$\leq 9.5$	$\geq 16.5$
Male	$\leq 11.5$	$\geq 18.5$
Hematocrit (%)		
Female	$\leq 32$	$\geq 50$
Male	$\leq 37$	$\geq 55$
Red Blood Cells ( $\times 10^{12}/L$ )		
Female	$\leq 3.5$	$\geq 6.0$
Male	$\leq 3.8$	$\geq 7.0$
White Blood Cells ( $\times 10^9/L$ )	$\leq 2.8$	$\geq 16.0$
Platelet Count ( $\times 10^9/L$ )	$\leq 75$	$\geq 700$
Eosinophils (%)		$\geq 10$
Basophils (%)		$\geq 10$
Lymphocytes (%)		$\geq 75$
Monocytes (%)		$\geq 15$
Neutrophils (%)	$\leq 15$	
Bands (%)		$\geq 10$
Mean Corpuscular Volume (fL)	$\leq 0.8 \times LLN$	$\geq 1.2 \times ULN$
Mean Corpuscular Hemoglobin Concentration (g/dL)	$\leq 0.8 \times LLN$	$\geq 1.2 \times ULN$
Atypical Lymphocytes (%)		$\geq 5$
Prothrombin Time (sec)		$\geq 2 ULN$
Partial Thromboplastin Time (sec)		$\geq 2 ULN$

LLN = Lower limit of normal      ULN = Upper limit of normal

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Chemistry	Below Limit	Above Limit
Albumin (g/dL)	$\leq 2.5$	
Alkaline Phosphatase (IU/L)		$\geq 3 \times \text{ULN}$
Bicarbonate (mEq/L)	$\leq 12$	$\geq 38$
BUN (mg/dL)		$\geq 30$
Calcium (mg/dL)	$\leq 8.2$	$\geq 12$
Chloride (mEq/L)	$\leq 90$	$\geq 118$
Cholesterol (mg/dL)		$\geq 600$
Creatinine (mg/dL)		$\geq 2.0$
Direct Bilirubin (mg/dL)		$\geq 2.0$
Glucose (mg/dL)	$\leq 45$	$\geq 175$
LDH (IU/L)		$\geq 3 \times \text{ULN}$
Inorganic Phosphorus (mg/dL)	$\leq 1.7$	$\geq 5.5$
Potassium (mEq/L)	$\leq 3.0$	$\geq 6.0$
SGOT/AST (IU/L)		$\geq 3 \times \text{ULN}$
SGPT/ALT (IU/L)		$\geq 3 \times \text{ULN}$
Sodium (mEq/L)	$\leq 126$	$\geq 156$
Total Bilirubin (mg/dL)		$\geq 2.0$
Total Protein (g/dL)	$\leq 4.5$	$\geq 10$
Triglycerides (mg/dL)		$\geq 600$
Uric acid (mg/dL)		
Female		$\geq 8.5$
Male		$\geq 10.5$

ULN = Upper limit of normal

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### Appendix I (Cont.)

Urinalysis	Below Limit	Above Limit
Specific Gravity	$\leq 1.001$	$\geq 1.030$
PH	$\leq 4$	$\geq 9$
Protein		$\geq 3+^*$ ( $\geq 10$ )
Ketones		$\geq 3+^*$
RBC		
Female		$\geq 10/\text{hpf}$
Male		$\geq 8/\text{hpf}$
WBC		$\geq 10/\text{hpf}$ ( $\geq 2+$ )
Casts		$\geq 9$
Glucose		$\geq 3+^*$
<b>Oral Body Temperature</b>		
Temperature	Low: decreased $\geq 2^\circ\text{F}$ from baseline High: $\geq 101^\circ\text{F}$	
<b>Body Weight</b>		
Weight	Low: decreased $\geq 15\%$ from baseline High: increased $\geq 15\%$ from baseline	
<b>Supine or Sitting Vital Signs</b>		
Systolic Blood Pressure	Low: $\leq 90$ mmHg and decreased $\geq 30$ from baseline High: $\geq 180$ mmHg and increased $\geq 40$ from baseline	
Diastolic Blood Pressure	Low: $\leq 50$ mmHg and decreased $\geq 20$ from baseline High: $\geq 105$ mmHg and increased $\geq 30$ from baseline	
Heart Rate	Low: $\leq 50$ bpm and decreased $\geq 30$ bpm from baseline High: $\geq 120$ bpm and increased $\geq 30$ bpm from baseline	

\*  $\geq 3+$  on a scale with 4+ being the maximum value

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<b>Electrocardiogram</b>	
PR Interval	High: $\geq 210$ msec
QRS Duration	Low: $\leq 50$ msec
	High: $\geq 150$ msec
QT Interval	Low: $\leq 200$ msec
	High: $\geq 500$ msec
QTc Interval*	Low: $\leq 200$ msec
	High: $\geq 500$ msec
Heart Rate	Low: $\leq 50$ bpm and decreased $\geq 30$ bpm from baseline
	High: $\geq 120$ bpm and increased $\geq 30$ bpm from baseline

\* QTc calculated as QT divided by the square root of RR interval

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